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# CONTENTS OF VOLUME 40

JULY 1948. NUMBER 1

	PAGE
Studies in Experimental Ocular Tuberculosis: XI. Effect of "Promin" and "Promizole" in Experimental Ocular Tuberculosis in the Normal Rabbit. Alan C. Woods, M.D., and Earl L. Burky, M.D., Baltimore.....	1
Granular Cell Myoblastoma of the Orbit. John H. Dunnington, M.D., New York.....	14
Experimental Investigation of the Pathogenicity of Diphtheroids Isolated from the Human Conjunctiva. Charles Weiss, Ph.D., M.D., Philadelphia, and Marian C. Shevky, A.B., and Isabella H. Perry, M.D., San Francisco.....	23
Contaminated Ophthalmic Ointments. Louis Lehrfeld, M.D., and Edward J. Donnelly, M.D., Philadelphia.....	39
Clinical Experiments with New Ways of Influencing Intraocular Tension: I. Effect of Rice Diet. Frederick W. Stocker, M.D.; Lawrence B. Holt, M.D., and James W. Clower, M.D., Durham, N. C.....	46
Tumors of the Optic Nerve: Long Survival in Three Cases of Intracranial Tumor. Captain Marvin Posner, Medical Corps, Army of the United States, and Gilbert Horrax, M.D., Boston.....	56
News and Notes.....	77
Society Transactions:	
American Ophthalmological Society.....	78

AUGUST 1948. NUMBER 2

Necrosis of Intraocular Tissues. Bernard Samuels, M.D., New York.....	101
Incidence of Defective Color Vision Among Psychotic Patients. LeGrand H. Hardy, M.D.; Gertrude Rand, Ph.D., and M. Catherine Rittler, A.B., New York.....	121
Preplacement of Air in Cyclodialysis. Sol Rome, M.D., and Raphael Koff, M.D., Los Angeles.....	134
Deep Keratitis Associated with Atypical Lichen Planus: Report of a Case. J. Goldsmith, M.D., New York.....	138
An Aid in Detecting Trachoma-like Inclusion Bodies in the Conjunctiva. Martin Bodian, M.D., Brooklyn.....	147
Occlusion of the Cilioretinal Artery. Jesse M. Levitt, M.D., Brooklyn.....	152
"Silent" Dacryocystitis. Frederick H. Theodore, M.D., New York.....	157
The History of the Dartmouth Eye Institute. Hermann M. Burian, M.D., Boston .....	163
Di-Isopropyl Fluorophosphate (D F P) in Treatment of Glaucoma: Further Observations. Irving H. Leopold, M.D., and P. Robb McDonald, M.D., Philadelphia .....	176
Lattice Type of Hereditary Corneal Degeneration: Report of Five Cases, Including One of a Child of Two Years. Frederick C. Stansbury, M.D., Syracuse, N. Y.....	189

## AUGUST—Continued

	PAGE
Abstracts from Current Literature.....	218
Obituaries:	
H. Maxwell Langdon, M.D.....	235
Book Reviews.....	237

## SEPTEMBER 1948. NUMBER 3

Successful Diathermy Treatment of Recurring Retinal Hemorrhage and Retinitis Proliferans: Report of a Case. F. H. Verhoeff, M.D., Boston.....	239
Ocular Changes Associated with Scrub Typhus: A Study of Four Hundred and Fifty-One Patients. Harold G. Scheie, M.D., Philadelphia.....	245
Nearly One Hundred Years of the Ophthalmoscope. Professor M. Sachs, Vienna, Austria.....	268
Cholinesterase in the Aqueous of the Eye. Norman S. Jaffe, M.D., Brooklyn..	273
Electrophoretic Patterns of Concentrated Aqueous Humor of Rabbit, Cattle and Horse. Ludwig von Sallmann, M.D., and Dan H. Moore, M.D., New York.....	279
Effect of Intramuscular Administration of Morphine, Atropine, Scopolamine and Neostigmine on the Human Eye. Irving H. Leopold, M.D., and Julius H. Comroe Jr., M.D., Philadelphia.....	285
Delayed Keratitis Due to Mustard Gas (Dichlorodiethyl Sulfide Burns): Report of Two Cases. Walter S. Atkinson, M.D., Watertown, N. Y.....	291
Treatment of Ocular Syphilis with Penicillin. Curtis D. Benton Jr., M.D., and Albert Heyman, M.D., Atlanta, Ga.....	302
Diagnosis of Retinoblastoma. Arthur J. Bedell, M.D., Albany, N. Y.....	311
Practical Application of the Denervated Iris. Norman S. Jaffe, M.D., Brooklyn	317
Clinical Aniseikonia. John P. Macnie, M.D., New York.....	326
Medical Versus Surgical Treatment of Glaucoma. Louis Lehrfeld, M.D., Philadelphia .....	332
Retrolental Fibroplasia: A Preliminary Report. A. C. Unsworth, M.D., Hartford, Conn.....	341
Clinical Notes:	
A Simple Appositional Suture for Use in Operations for Cataract. Charles A. Perera, M.D., New York.....	347
Fixation Light. John V. McMackin, M.D., Miami, Fla.....	351
Abstracts from Current Literature.....	353
Book Reviews.....	369
News and Notes.....	370

## OCTOBER 1948. NUMBER 4

The Blindspot Syndrome. Kenneth C. Swan, M.D., Portland, Ore.....	371
Use of Roentgen Therapy for Retinal Diseases Characterized by New-Formed Blood Vessels (Eales's Disease; Retinitis Proliferans): A Preliminary Report. Jack S. Guyton, M.D., Baltimore, and Algernon B. Reese, M.D., New York.....	389

## OCTOBER—Continued

	PAGE
Studies in Experimental Ocular Tuberculosis: XII. Effect of Streptomycin and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit. Alan C. Woods, M.D., and Ronald M. Wood, B.S., Baltimore....	413
Retinal Tumor Associated with Neurofibromatosis (von Recklinghausen's Disease): Report of a Case. Fritz J. Bloch, M.D., New York.....	433
Vision in Strabismus: A Preliminary Report. Frank Costenbader, M.D.; Dorothy Bair, B.A., and Alice McPhail, R.N., Washington, D.C.....	438
Conical Cornea and Mongolism. Andrew Rados, M.D., Newark, N. J.....	454
Book Reviews.....	479

## NOVEMBER 1948. NUMBER 5

Ophthalmoscopy and Operations for Reduction of High Blood Pressure. Arthur J. Bedell, M.D., Albany, N. Y.....	483
Electronic Flash (Gas Discharge) Tube in Photography of the Anterior Segment of the Eye. Robert Russell Trotter, M.D., and W. Morton Grant, M.D., Boston.....	493
Esthetic Correction of Unilateral Anophthalmos by Ophthalmoprostheses. Phelps J. Murphey, D.D.S.; F. H. Newton, M.D.; Cecil Stell, M.D., and Peggy Parker Hawk, B.A., Dallas, Texas.....	497
Nonperforating Thermometric Cyclodiathermy in Treatment of Hypertensive Uveitis. L. Weekers, M.D., and R. Weekers, M.D., Liège, Belgium.....	509
Lymphosarcoma of the Eyelid: Report of Case, with Death in Forty Days. Frederick C. Stansbury, M.D., Syracuse, N. Y.....	518
Infection of the Cornea Due to Herpes Simplex: An Experimental Study. James L. McGraw, M.D., Syracuse, N. Y.....	531
Invasion of the Optic Nerve by Retinoblastoma. Algernon B. Reese, M.D., New York.....	553
Clinical Course of Ocular Complications of Arachnodactyly. Ralph I. Lloyd, M.D., Brooklyn.....	558
Lipemia Retinalis Associated with Essential Hyperlipemia. Erwin E. Grossmann, M.D., and John B. Hitz, M.D., Milwaukee.....	570
News and Notes.....	574
Society Transactions:	
Société Française d'Ophtalmologie.....	575
Book Reviews.....	577

## DECEMBER 1948. NUMBER 6

Localizing Value of Visual Fields in Patients with Early Chiasmal Lesions. Francis H. Adler, M.D.; George Austin, M.D., and Francis C. Grant, M.D., Philadelphia.....	579
The Cornea. William M. Hart, M.D., Ph.D., and Bruce F. Chandler, M.D., Philadelphia:	
I. Swelling Properties of the Fibrous Tunic of the Eye.....	601
II. Factors Affecting the Transmission of Visible Light by the Fibrous Tunic of the Eye.....	612

DECEMBER.—*Continued*

	PAGE
Hypercalcemia and Band Keratopathy: Report of Nineteen Cases. David G. Cogan, M.D.; Fuller Albright, M.D., and F. C. Bartter, M.D., Boston...	624
Dermoid and Epidermoid Tumors of the Orbit. Raymond L. Pfeiffer, M.D., and Russell J. Nicholl, M.D., New York.....	639
A Simple Operation for Entropion. Jay B. V. Butler, M.D., Portland, Ore...	665
Practical Application of Surface-Active Drugs in Ophthalmology. J. B. Feldman, M.D.; P. DeLong, M.D., and C. P. Brown, M.D., Philadelphia....	668
Operation for Congenital Cataract. Otto Barkan, M.D., San Francisco.....	680
Choroidoretinal Degeneration: A Sex-Linked Form in Which Heterozygous Women Exhibit a Tapetal-like Retinal Reflex. Harold F. Falls, M.D., and C. W. Cotterman, Ph.D., Ann Arbor, Mich.....	685
A Method of Preservation of Animal Eyes. Paul M. Runge, M.D., Boston...	704
General Index.....	707

## STUDIES IN EXPERIMENTAL OCULAR TUBERCULOSIS

### XI. Effect of "Promin" and "Promizole" in Experimental Ocular Tuberculosis in the Normal Rabbit

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AND

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IN A PREVIOUS paper,<sup>1</sup> the effect of treatment with two sulfone compounds, "promin" (the sodium salt of *p*, *p'*-diaminodiphenylsulfone-*N,N'*-didextrose sulfonate) and "promizole" (4,2-diaminophenyl-5'-thiazoylsulfone), on experimental ocular tuberculosis in the immune-allergic rabbit was reported. It was found that both these drugs exerted a strongly deterrent action on the course of the ocular tuberculosis. This deterrent action became evident after the third week of treatment. While histologic evidences of tuberculosis persisted in the healed eyes, the lesions were much fewer and less severe than in the control eyes. In transmission experiments, in which tissue from the eyes of treated rabbits was inoculated into normal rabbits, only one eye of the treated animals was found to be infectious.

These experiments were performed on immune-allergic rabbits—animals with a preexisting systemic tuberculosis at the time the eyes were inoculated. As a result of the systemic infection, these rabbits had a well developed acquired resistance, or immunity, to reinfection. It was not clear whether the deterrent action of the sulfone compounds noted in this experiment was due to a bactericidal action or to degradation or attenuation of the virulence of the organisms, thus allowing the resistance of the host to become more effective. The experiments here reported were undertaken with the idea of clarifying this point. The plan and execution of the experiments were identical with those previously reported, except that normal rabbits, in which no acquired immunity was present, were used as the experimental animals.

From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University.

This work was supported in part by a grant from the John and Mary R. Markle Foundation.

1. Woods, A. C., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: X. Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, *Arch. Ophth.* 39:471 (April) 1948.

## TECHNIC

Sixty normal rabbits, of mixed breed and sex, were inoculated on Dec. 13, 1946 in the anterior chamber of the left eye with 0.2 cc. of the paper filtrate of a six week old culture of a virulent strain of human tubercle bacilli. There was little or no reaction to the inoculation, and when the rabbits were examined one week later, on December 20, all eyes were recorded as showing no clinical activity. On December 27, evidence of ocular tuberculosis, consisting of small tubercles in the iris or in the cornea, with low grade pericorneal congestion, was present in all rabbits. The rabbits were then divided into three groups of the same number. The animals in group 1 were untreated and served as controls; those in group 2 were treated with "promin," and those in group 3, with "promizole." A suspension of the "promin" and "promizole" in water was sprayed over the pellets with which the rabbits were fed, so that a 1 per cent concentration of the drug was obtained in the food. A little "karo" syrup was added, and the pellets were dried. Each rabbit consumed about 1,000 Gm. of this mixture each week, or an approximate daily dose of 1.5 Gm. of "promin" or "promizole." Estimations of the concentration of the drugs in the blood were made by Dr. E. K. Marshall, of the department of pharmacology, on January 25, and again on April 15, at the close of the experiment. In these two estimates, the concentrations of "promin" were 0.2 and 4.4 mg. per hundred cubic centimeters, and those of "promizole," 0.5 and 2.4 mg. With the high dosage of the sulfone compounds, a greater concentration in the blood might properly have been expected. The only explanation for the relatively low figures consistently obtained is that the absorption of the drug from the gastrointestinal tract must have been low.

Treatment was begun on December 27. At the beginning of the experiment the average weight of the rabbits was as follows: group 1, 2,800 Gm.; group 2, 2,324 Gm., and group 3, 2,373 Gm. At the end of the experiment the average weights were as follows: group 1, 3,363 Gm.; group 2, 3,363 Gm., and group 3, 2,954 Gm. In short, all animals appeared to thrive on the diet. The rabbits were examined each week, and the degree of ocular tuberculosis was noted in the same manner as that described in the previous papers of this series. The average reading for each group was plotted each week on coordinate paper, so that a comparative graph of the course of the disease could be obtained.

By April 11, the disease in all three groups had pretty well run its course; the experiment was then terminated, the animals were killed and the eyes were removed. All ruptured eyes were sectioned for histologic study. The unruptured eyes in each group were used for transmission experiments.

## OBSERVATIONS

*Clinical Results.*—The composite results are shown in figure 1. Treatment in groups 2 and 3 was started at the end of the second week. For two weeks thereafter there was no noticeable difference between the controls and the treated groups. At the end of the second week of treatment, the disease in the two treated groups became slightly less active than that in the control group, and this lessened activity in the treated groups was maintained throughout the course of the experiment, becoming more marked after the eighth week. The maximum difference was noted at the end of the eleventh week, when the control eyes showed an average

estimated clinical activity of 3.0 and the two treated groups an activity of 1.4. By this time, however, the greater number of the eyes had ruptured, and several animals had died of intercurrent infections. Thus, in the control group, at the end of the eleventh week, there were 19 survivors, and in 17 of these the inoculated eyes had become buphthalmic and had ruptured; in the group treated with "promin," all animals had survived, and the eyes of 17 had become buphthalmic and 13 had ruptured; in the group treated with "promizole," there were 17 survivors, and 14 eyes had ruptured. After rupture, a few of the eyes became phthisical; several others were secondarily infected, and in the remainder the corneas became so heavily vascularized that any accurate estimation of the degree of tuberculosis involvement was difficult or impossible. This course of ocular tuberculosis is the usual one in normal rabbits and is in sharp contrast with the course of the disease in the

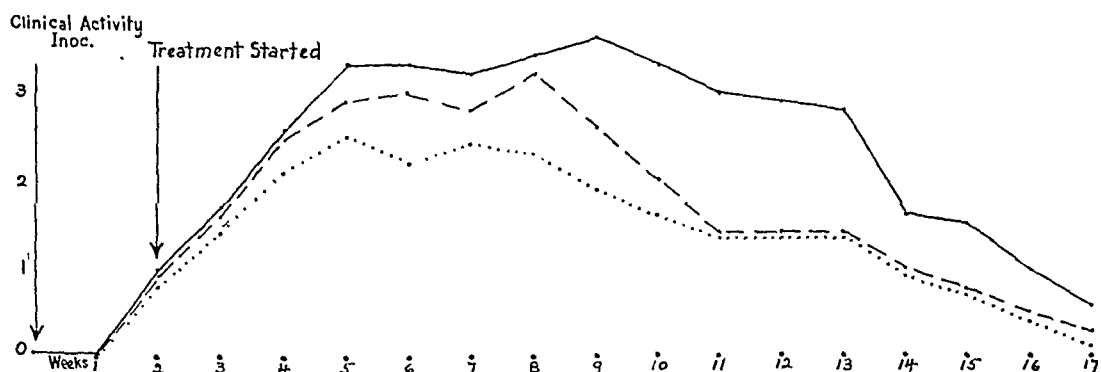


Fig. 1.—Clinical results of treatment with "promin" and "promizole" in normal rabbit eyes. The ratings for the control group are indicated by the solid line; those for the rabbits treated with "promin," by the line of dashes, and those for the rabbits treated with "promizole," by the line of dots.

immune rabbit. In immune animals, rupture of the globe practically never occurs, and, except for isolated tubercles or infiltrates with local vascularization, the corneas remain clear. Therefore, after the eleventh week, in these normal rabbits there was little to be seen clinically except the vascular reaction and acute inflammation. This inflammation steadily decreased in all three groups; and at the conclusion of the experiment, at the seventeenth week, the average activity was estimated as 0.6 for the control group, 0.3 for the "promin"-treated group and 0.12 for the "promizole"-treated group. However, the eyes were so badly scarred and heavily vascularized that in the later stages of the experiment the evaluation of the severity of the disease was little more than an estimation of acute inflammatory reactions and the obvious damage done to the eyes. However, in summary, it may be stated that clinical examination of the eyes in the three groups showed that in general the inflammatory picture appeared less severe in the two treated groups and subsided earlier than in the untreated group.



*Histologic Results.*—At the conclusion of the experiment, 1 rabbit in the control group, none in the “promin”-treated group and 3 in the “promizole”-treated group had died of intercurrent infections. All the surviving rabbits, 19 in group 1, 20 in group 2 and 17 in group 3, were killed and the eyes enucleated. As before stated, the ruptured eyes



Fig. 2 (control eyes).—A, large tubercle of cornea, detachment of Descemet's membrane and tuberculous infiltration tissue in anterior chamber; B, tuberculous infiltration tissue in vitreous chamber.  $\times 80$ .

(17 in group 1, 13 in group 2 and 14 in group 3) were sectioned for study, and the unruptured eyes were used for transmission experiments. The histologic pictures in the three groups were as follows:

GROUP 1 (Controls): With 1 exception, all the control eyes showed the picture of advanced, uncontrolled caseous tuberculosis, with large

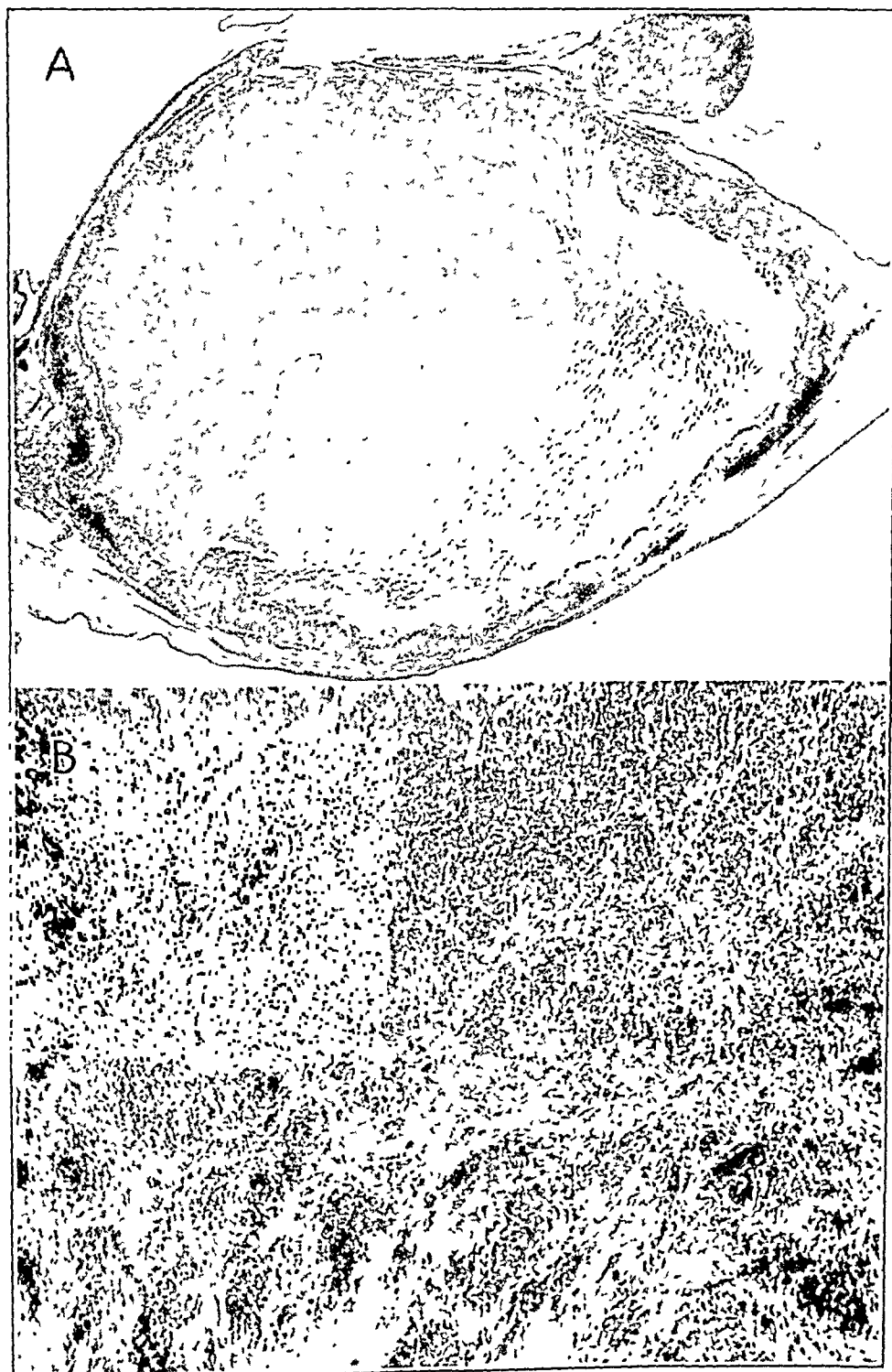


Fig. 3 (control eyes).—A, tuberculoma of ciliary body and necrosis of sclera;  $\times 12$ . B, ciliary area in ruptured phthisical eye, showing active tuberculosis;  $\times 80$ .

tubercles in the cornea, iris and ciliary body and with tuberculous infiltration tissue of epithelioid and giant cells invading both the anterior and the vitreous chamber. Figures 2 to 4 illustrate the typical pictures presented by this group. Figure 2*A* shows a tubercle of the cornea, with tuberculous infiltration tissue causing detachment of Descemet's membrane and invading the anterior chamber; figure 2*B*, tuberculous infiltration tissue invading the vitreous cavity; figure 3*A*, a buphthalmic eye with a large tuberculoma of the ciliary body invading the sclera; figure 3*B*, the ciliary area in a ruptured phthisical eye, almost filled with



Fig. 4 (control eye).—Ciliary area in ruptured phthisical eye, showing activity subsiding and early fibrosis;  $\times 80$ .

tuberculous tissue, and figure 4, a similar picture, but with the process somewhat burned out, with early fibrosis. The characteristic of all the eyes in this group was the spreading, unrestricted character of the tuberculous lesions and the tendency of tuberculous tissue, consisting chiefly of epithelioid and giant cells, to invade the cavities of the eye.

GROUP 2 (Eyes Treated with "Promin"): Practically all these eyes showed active tuberculosis, but in general the process was somewhat less active than that in the controls. Infiltration of the anterior and vitreous cavities was present in several eyes. Figure 5*A* shows the eye in which infiltration of the vitreous chamber was most prominent, but the infiltration was definitely less extensive than in the controls; figure 5*B* shows a tuberculoma of the ciliary body with caseation and necrosis. Figure 6*A* shows a phthisical eye with generalized tuberculosis; but, again, the

process appeared less robust than in similar control eyes (fig. 3 *B*). Figure 6 *B* shows a phthisical eye in which the process was almost inactive, only small areas of activity being noted in the ciliary body.

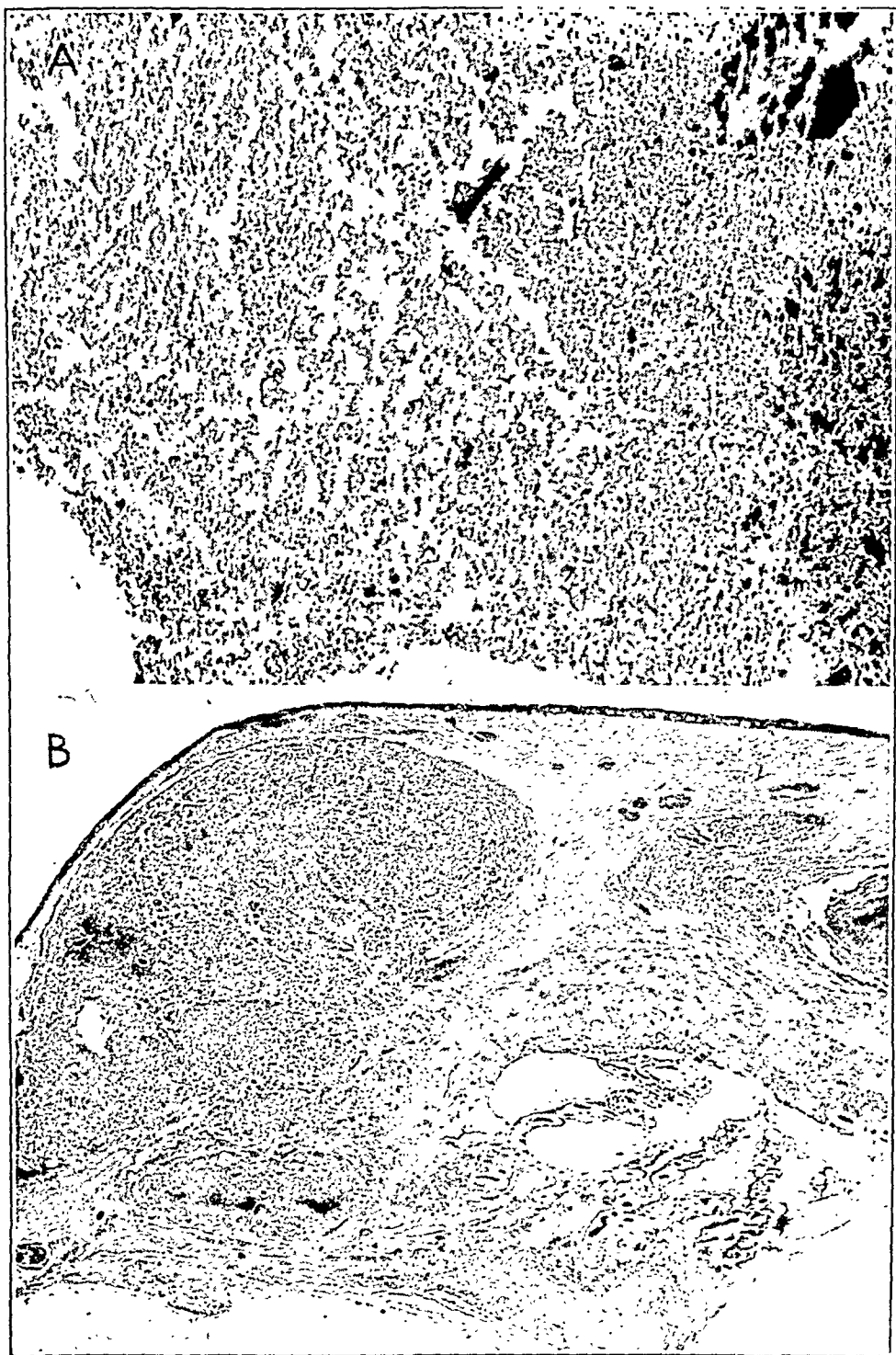


Fig. 5 (eyes treated with "promin").—*A*, tuberculous infiltration tissue in vitreous chamber;  $\times 80$ . *B*, tuberculoma of ciliary body, with caseation and fibrosis;  $\times 12$ .

On a numerical scale, the degree of tuberculous involvement in the eyes of this group of rabbits was rated as about 3, as compared with a rating of 4 given the control group.

GROUP 3 (Eyes Treated with "Promizole"): Again, in this group all the eyes showed pronounced active tuberculosis. If anything, the degree of activity in this group was slightly greater than in the rabbits



Fig. 6 (eyes treated with "promin").—A, ciliary area of phthisical eye, with early fibrosis; B, small areas only of activity in ciliary area.  $\times 80$ .

treated with "promin," but, again, it appeared less than in the control group. On a numerical scale, 3+ would be a fair rating. Figure 7 A shows one of the eyes, with the most active process in this group, with

tuberculous infiltration tissue filling the anterior chamber. Figure 7 *B* shows another eye, with extreme activity, with tuberculosis tissue invading the vitreous. However, in this series, tuberculous infiltration of the



Fig. 7 (eyes treated with "promizole").—*A*, tuberculosis of cornea, with detachment of Descemet's membrane and tuberculous infiltration tissue in anterior chamber; *B*, tuberculous infiltration tissue in vitreous chamber.  $\times 80$ .

vitreous was not so extreme as in the control group. Figure 8 *A* shows a fairly well circumscribed necrotic tubercle of the cornea, while figure 8 *B*

shows one of the better eyes, with the relatively clear cornea showing only minor tubercles and collections of leukocytes.

*Transmission Experiments.*—Two unruptured eyes in group 1, 7 unruptured eyes in group 2 and 3 unruptured eyes in group 3 were used

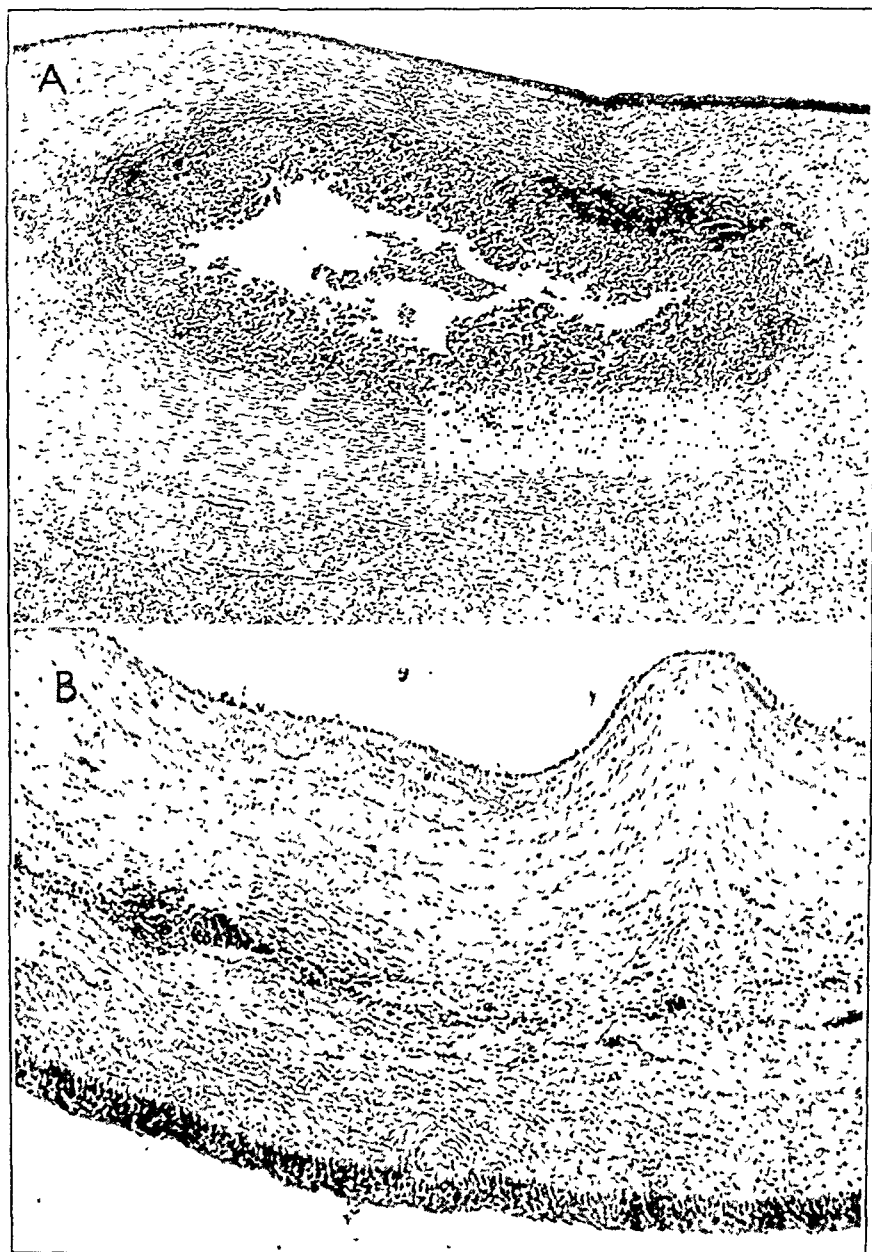


Fig. 8 (eyes treated with "promizole").—A, circumscribed, necrotic tubercle in cornea;  $\times 40$ . B, trace of tuberculosis in cornea;  $\times 80$ .

in transmission experiments, as before described. These eyes were opened under aseptic precautions, and the uveal tract was removed and ground up with sand in a sterile mortar with a little saline solution. The supernatant fluid was then inoculated into the anterior chamber of normal



rabbits. The rabbits were kept under observation for three months for the development of clinical ocular tuberculosis. They were then killed and the eyes sectioned. In every instance the normal eyes inoculated with

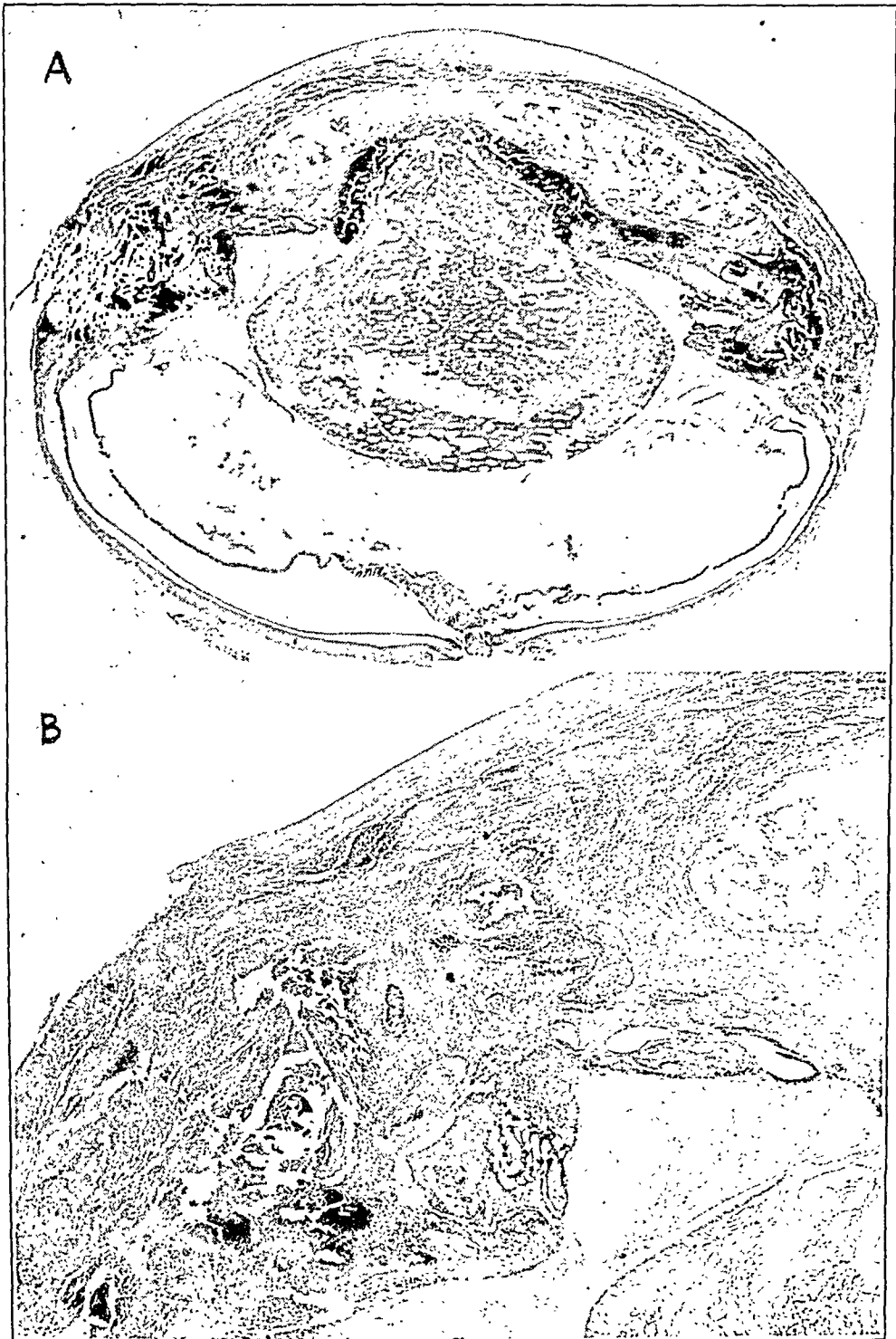


Fig. 9.—*A*, eye used in transmission experiments, showing advanced tuberculosis and invasion of anterior and posterior chambers;  $\times 4\frac{1}{2}$ . *B*, ciliary region of same eye as that shown in *A*;  $\times 12$ .

material from the eyes of these rabbits presented the typical clinical picture of ocular tuberculosis in the normal animal. The incubation period for each animal was roughly the same—eight to twelve days from the



time of inoculation to the onset of symptoms. The course of the disease was rapid in the secondarily inoculated rabbits, and the histologic picture was similar to that of the control group, as previously described, the eyes showing advanced, diffuse tuberculosis as the predominating lesion. As might be expected from the nature of the inoculation, several eyes showed evidence of secondary infection, manifested by a few small abscesses throughout the eye. Figure 9 (*A* and *B*) shows the typical picture in a rabbit used for transmission experiments.

#### COMMENT

It is apparent that any deterrent action exerted by the "promin" and "promizole" treatment in these normal rabbits was extremely slight. While it is true that both the clinical and the histologic lesions in the eyes of the treated rabbits were slightly less severe than in the control eyes, the difference was not striking. The diseased eyes of both the controls and the treated rabbits must have contained large numbers of virulent bacilli at the end of the experiment. This was manifested by the transmission experiment, in which extensive tuberculosis developed in the eyes of the secondarily inoculated rabbits after a short incubation period of eight to twelve days.

The obvious explanation of the difference in results in the normal and in the immune-allergic rabbits is that the tuberculous infection in the normal rabbits was so massive that it was beyond the power of the "promin" and "promizole" to control. It is noteworthy that the onset of the ocular tuberculosis in the eyes of the normal rabbits was rapid, the first symptoms appearing two weeks after inoculation, in contrast with an incubation period of six weeks for the immune-allergic animals. This difference was present despite the fact that the eyes of the immune-allergic rabbits received a much more massive inoculation.

While treatment was instituted in both groups at relatively the same time with respect to onset of symptoms, nevertheless, the ocular lesions developed with much greater rapidity in the normal rabbits; and after three weeks of treatment, at which time the first deterrent action was noted in the immune-allergic rabbits, the degree of clinical ocular tuberculosis in the normal rabbits was greater than in the immune-allergic series. Thus, if one accepts the indication of the first experiment, i.e., that three weeks' treatment with this dose is necessary before any deterrent action can be expected of these sulfone compounds, it is evident that as regards massiveness of infection alone a vastly greater therapeutic task was imposed in this experiment than in the previous experiment.

The simple facts are that in the presence of such a massive infection, in animals without systemic immunity, the "promin" and "promizole" exhibited only a slight deterrent action on the tuberculous process, whereas with a less extensive and a restrained infection, together with a well

developed systemic immunity, these sulfone compounds exhibited a strongly deterrent action on the ocular disease.

This observation does not give a clear answer to the original question, namely, whether the deterrent action of "promin" and "promizole" was due to a direct bactericidal action on the bacilli or to a depression and attenuation of their virulence, thus allowing the resistance of the host to become more effective. It is, however, strongly indicative. In the presence of massive infection, a slight deterrent action was still noticeable, while in the presence of a less intense and a restrained infection the deterrent action was pronounced. Thus, it would appear that "promin" and "promizole" exert, by one means or another, a limited bactericidal action against the *Mycobacterium tuberculosis*. When the dissemination and propagation of the bacilli are restrained by a systemic immunity, this bactericidal action is clearly evident; when the dissemination and growth of the bacilli are unrestrained, there results an infection so massive that it is beyond the therapeutic range of the sulfone drugs. It must be granted that an almost equally good case can be made for the second alternative, i.e., that these sulfone compounds depress the growth and virulence of the organisms, thus allowing the systemic immunity to become more effective. However, when one considers the over-all picture, notably, the observation that the deterrent action of these sulfone compounds was pronounced only when the growth and dissemination of the organisms was first restrained by the systemic immunity, it appears more logical to conclude that the deterrent action is due to a limited bactericidal effect.

#### CONCLUSIONS

"Promin" and "promizole," used in the same dose as that which had a pronounced deterrent effect on ocular tuberculosis in the immune-allergic rabbit, produced only a slight deterrent action on ocular tuberculosis in the normal animal. This slight action was first noticed clinically after two weeks of treatment and was somewhat more pronounced after eight weeks of treatment. There was, however, only a slight difference in the degree and extent of the disease when the eyes of the control and those of the treated animals were examined histologically. All transmission experiments with the treated animals gave positive results, indicating that large numbers of living virulent bacilli were still present in the eyes.

An examination of the results of this experiment, and of the similar experiment with immune-allergic rabbits, indicates that "promin" and "promizole" probably have a limited bactericidal effect on the tubercle bacillus, this action becoming clearly evident only when the tuberculous process is so restrained by a systemic immunity that it is brought within the therapeutic range of these sulfone compounds.

## GRANULAR CELL MYOBLASTOMA OF THE ORBIT

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NEW YORK

WITHIN recent years much has been written by the pathologists about a type of tumor variously designated by the names "myoblastic myoma," "myoblastoma," "rhabdomyoma" and "granular cell myoblastoma." Confusion still exists as to the correct terminology, but all are agreed on the pathologic picture of this tumor type. Using the name myoblastoma (*Myoblastenmyom*), Abrikossoff,<sup>1</sup> in 1926, first described this peculiar tumor of striated muscle tissue. The characteristic microscopic features may be summarized as follows: (1) large polyhedral cells, 20 to 60 microns in diameter, constitute a nodular accumulation of neoplastic cells; (2) the cytoplasm stains only faintly with eosin and contains many coarse neutrophilic granules; (3) cross or longitudinal striations are rarely seen; (4) the nuclei are small and never show the irregularity associated with malignancy; (5) the tumor cells, individually or in groups, are surrounded by a thin network of connective tissue fibers; (6) the cells are devoid of fat. Later, in 1931, he<sup>2</sup> described the histologic features of four different varieties of this tumor. Ravich, Stout and Ravich<sup>3</sup> differentiated these types in the following manner:

(1) The typical form made up of round, egg-shaped, or elongated myoblasts from 20 to 25 microns long with granules but without longitudinal or cross striations; (2) a variation of the first type in which some cells show longitudinal or cross striations; (3) a hypertrophic form with cells from 40 to 60 microns and sometimes multinucleated. These first three groups are all composed of granular cells and all are benign tumors; (4) malignant myoblastic myoma in which the

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Read before the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 6, 1947.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology of the Presbyterian Hospital of New York.

1. Abrikossoff, A.: Ueber Myome ausgehend von der quergestreiften willkürlichen Muskulatur, *Virchows Arch. f. path. Anat.* **260**:215-233, 1926.

2. Abrikossoff, A. I.: Weitere Untersuchungen über Myoblastenmyome, *Virchows Arch. f. path. Anat.* **280**:723-740, 1931.

3. Ravich, A.; Stout, A. P., and Ravich, R. A.: Malignant Granular Cell Myoblastoma Involving the Urinary Bladder, *Ann. Surg.* **121**:361-372 (March) 1945.

myoblasts are not granular, but assume atypical aspects and vary in size so that the tumor resembles a polymorphous sarcoma.

It is the fourth type which has led to the greatest amount of confusion. Most malignant tumors termed myoblastomas belong either to the rhabdomyosarcoma group or to the fourth subdivision of Abrikossoff. The cells of the latter type do not have a granular cytoplasm and rarely show the cross striations so characteristic of rhabdomyosarcoma.

Differentiation between granular cell myoblastoma and rhabdomyoma is not always easy; but, as pointed out by Cappell and Montgomery,<sup>4</sup> the relative absence of cross and longitudinal striations and the primitive nature of the myoblasts are diagnostic of granular cell myoblastoma. However, as emphasized by Stout,<sup>5</sup> the demonstration of cross striations in rhabdomyosarcoma is often a painstaking task, which will be successful only if the tumor material is well fixed and stained properly. Stout uses either Masson's trichrome stain, containing acid fuchsin; Heidenhain's hematoxylin stain or, if Zenker's solution is used for fixation, the phosphotungstic acid hematoxylin stain. Furthermore, he expressed the belief that high magnification is essential for the detection of these striations. This author expressed agreement with Howe and Warren<sup>6</sup> that myoblastomas should be separated from the rhabdomyosarcomas. Cappell and Montgomery,<sup>4</sup> on the other hand, stated that there is no absolute line of demarcation between these two growths and that transitions undoubtedly occur, which lead to difficulty in classification. A careful review of the recent literature convinces me that no uniformity in terminology exists at present, but that the two growths do present certain differences, not only in cellular structure but in clinical behavior. The rhabdomyoma is an infiltrative growth, always malignant or potentially so, while the granular cell myoblastoma is often encapsulated and is usually benign. The explanation offered by Cappell and Montgomery<sup>4</sup> for this apparent paradox, i.e., that myoblastoma, with its primitive character, is the more benign growth, lies in the presence or absence of any anaplastic or primitive round and short spindle cells in the primary growth. In myoblastoma the cellular structure is more homogeneous and uniform, and groups of highly anaplastic cells are absent. According to Ewing,<sup>7</sup> "a notable feature [in myoblastoma] is the tendency of the overlying skin to develop epidermoid carcinoma, which has sometimes proved malignant." Neither

4. Cappell, D. F., and Montgomery, G. L.: On Rhabdomyoma and Myoblastoma, *J. Path. & Bact.* 44:517-548 (May) 1937.

5. Stout, A. P.: Rhabdomyosarcoma of the Skeletal Muscles, *Ann. Surg.* 123: 447-472 (March) 1946.

6. Howe, C. W., and Warren, S.: Myoblastoma, *Surgery* 16:319-347 (Sept.) 1944.

7. Ewing, J.: *Neoplastic Diseases: A Treatise on Tumors*, ed. 4, Philadelphia, W. B. Saunders Company, p. 248.

of these growths presents any characteristic clinical appearance, and the differentiation is purely a histologic one. Xanthoma is another tumor with which this growth has been confused, but the absence of fat in the cells and the granular character of the cytoplasm in myoblastoma are the differentiating features.

The histogenesis of myoblastoma is much discussed in the literature, and there are two schools of thought with respect to its origin. It is believed by some to be a true neoplasm of immature, proliferating skeletal muscle cells (myoblasts) and by others to be a degenerative lesion, the cells being muscle fibers undergoing necrobiotic changes. Abrikossoff<sup>1</sup> first concluded that the tumors resulted from such a degenerative process following trauma or inflammation in striated muscle, but he later stated the belief that some of the tumors arise from primitive myoblasts, representing embryonic rests. The fact that myoblastomas most commonly arise from the muscular tissue of the tongue is strong support for the muscular origin of these growths, but they do occur in locations normally devoid of striated muscle tissue. For example, they have been reported in the gum of the newborn infant—a region devoid of muscle tissue of any sort. Their occurrence in such locations certainly bespeaks the dysontogenetic origin of some of these growths. Therefore, in view of the present inadequate knowledge, it would seem fair to say that some myoblastomas do arise from embryonic rests whereas others probably result from degenerative changes occurring in striated muscle tissue.

Myoblastic tumors are moderately common, and their distribution is widespread. According to the report of Crane and Tremblay,<sup>8</sup> of 162 such tumors, 37.6 per cent occurred in the tongue, and 20.4 per cent in the skin and subcutaneous tissue, while less frequently they were found in muscle and in the maxilla, breast, larynx, vocal cords, mandible, lip, trachea, bronchus, ear and alveolar process. Involvement of the orbit by such a new growth has rarely been observed. While the literature contains several references to granular cell myoblastoma having been found in the orbit, a critical analysis of these cases casts doubt on the accuracy of the diagnosis in some of them. For example, the first case reported in 1935 by Sjögren,<sup>9</sup> under the title "Myoblastoma Malignum Orbitae," is excluded. Here was described in detail the case of an 8 year old boy in which the clinical course, as well as the pathologic descriptions, was typical of rhabdomyosarcoma. The reports of Mitvalsky<sup>10</sup> and of Pieck<sup>11</sup>

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8. Crane, A. R., and Tremblay, R. G.: Myoblastoma (Granular Cell Myoblastoma or Myoblastic Myoma), *Am. J. Path.* **21**:357-375 (March) 1945.

9. Sjögren, H.: Myoblastoma malignum orbitae, *Arch. f. Ophth.* **134**:333-340, 1935.

10. Mitvalsky: Eine Ciliarkörpergeschwulst nebst Bemerkungen, *Arch. f. Augenh.* **28**:152-165, 1893-1894.

11. Pieck, C. F. M.: A So-Called Myoma of the Ciliary Body, *Ophthalmologica* **99**:471-475 (May) 1940.

of myoblastoma of the ciliary body are also to be questioned because the smooth muscle origin of the tumors would now classify them as leiomyomas. The first authentic case of orbital myoblastoma is that of von Bahr,<sup>12</sup> who observed this growth in the region of the lacrimal sac. The patient had had lacrimation for several years, with the development of a mass in the region of the lacrimal sac three weeks previously. At her first visit acute dacryocystitis with perforation was observed; this inflammation promptly subsided, leaving a firm tumor the size of a large pea. Extirpation of this growth was easily accomplished, without subsequent recurrence. Histologically the tumor consisted of bundles of large cells, 40 to 50 microns in length, with granular cytoplasm, large oval nuclei and no cross striations. At the periphery of the lesion the cells were larger and thicker with a yellower protoplasm and larger nuclei, resembling transitional forms of true muscle cells. Powell,<sup>13</sup> in reporting a case of primary granular cell myoblastoma of the ovary, referred to the presence of a metastatic nodule in the eyelid. In a recent article on myoblastoma of the eyelid, Cristini,<sup>14</sup> after recording a case of his own, referred to 5 previously reported cases. A careful study of the photomicrographs and pathologic descriptions of these tumors leaves one in a quandary as to their proper classification. It is possible that some belong to the rhabdomyoma group, since the presence of cross striations is frequently mentioned. If, however, one accepts these 6 cases as instances of granular cell myoblastoma, together with the case of von Bahr<sup>12</sup> and that of Powell,<sup>13</sup> the 2 cases here reported are the ninth and tenth on record. Since these tumors occur in such diffuse locations in the body, it is surprising that more of them have not been found in the orbit. With the hope, therefore, of focusing the attention of ophthalmic pathologists on tumors of this type, the present 2 cases are recorded.

#### REPORT OF CASES

CASE 1.—R. H., a white woman aged 36, was first seen Feb. 19, 1946. She gave a history of drooping of the right upper lid of nineteen months' duration, with proptosis first becoming evident ten months later. The condition progressed at first but had recently remained stationary. There were no inflammatory signs or discomfort except that produced by the ptosis. Examination revealed vision of 20/20 in each eye, 5 mm. of ptosis of the right upper lid and 6 mm. of exophthalmos of the right eye. The upward movements of this eye were seriously impaired. A firm, movable mass was palpable just under the upper orbital margin. A roentgeno-

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12. von Bahr, G.: A Case of Myoblastic Myoma of the Lacrimal Sac, *Acta ophth.* 16:109-115, 1938.

13. Powell, E. B.: Granular Cell Myoblastoma, *Arch. Path.* 42:517-524 (Nov.) 1946.

14. Cristini, G.: "Mioblastoma della palpebra" (studio anatomo-clinico), *Rassegna ital.d'ottal.* 15:207-223 (May-June) 1946.

gram of the orbit showed increased density of the soft tissues but no other changes. On February 26 a well encapsulated tumor, measuring 8 by 4 by 3 mm., was removed from the orbit by blunt dissection. The growth was in contact with the levator muscle but did not appear to arise from that muscle. Convalescence was

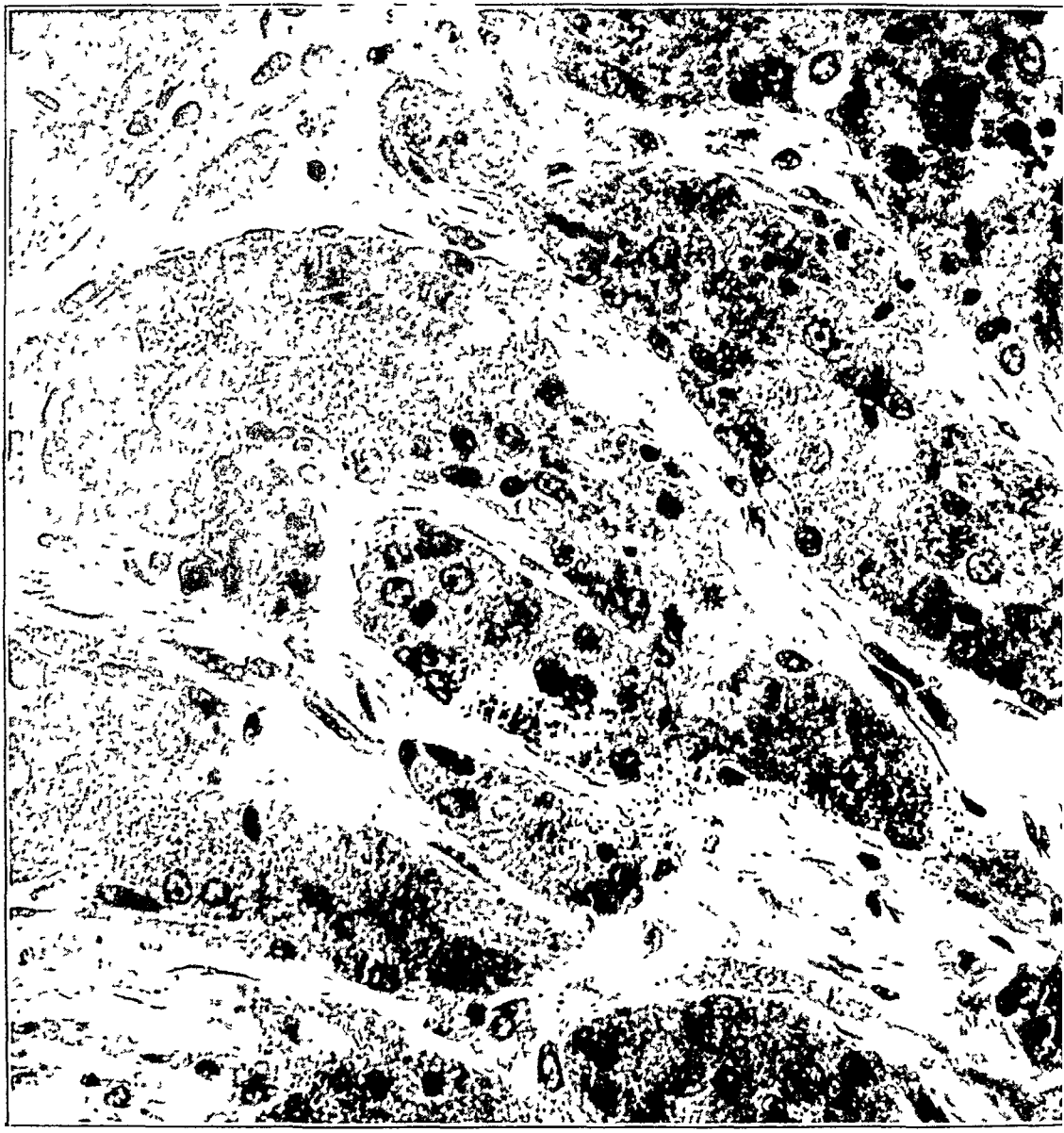


Fig. 1 (case 1) —Cords of tumor cells interspersed between connective tissue stroma. The cells show a large amount of granular cytoplasm. Trichrome stain; magnification, 500.

uneventful except that the ptosis became complete. On July 24, resection of 20 mm. of the levator muscle was performed. This resulted in an incomplete, but relatively satisfactory, correction of the ptosis. At the time of this operation no gross evidence of recurrence could be detected in the orbit, nor did the excised

portion of the levator muscle reveal any microscopic evidence of a new growth. The patient shortly thereafter returned to her home in Greece, so that no direct follow-up observation has been possible; judging from recent letters, however, she is still free from recurrence.

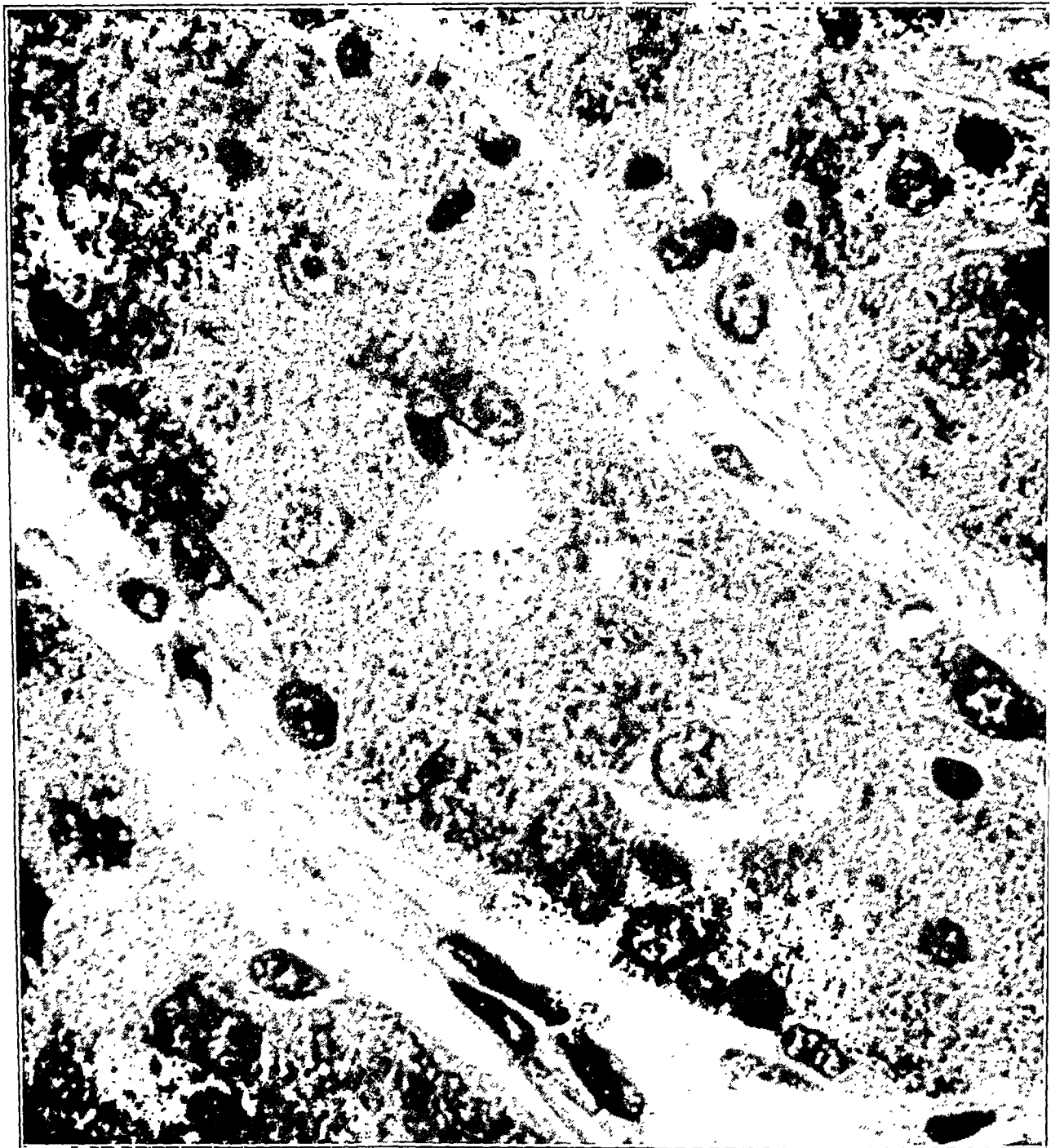


Fig. 2 (case 1).—Higher magnification ( $\times 1,000$ ) of a portion of figure 1.

The pathologic report on the tumor, as submitted by Dr. A. Purdy Stout, follows: "Microscopically the tumor was composed of differentiated granular myoblasts. They were arranged in cords, and the individual cells were rather large, with exquisitely and strikingly acidophilic granules in the abundant cytoplasm



surrounding the small, inactive nucleus. The growth was sharply circumscribed, but there appeared to be tumor cells in the fibrous sheath surrounding it, so that it was impossible to know whether or not the entire growth had been removed. Its appearance indicated that the growth was benign" (figs. 1 and 2).

CASE 2.—W. C., a white man aged 40, was first seen on April 2, 1945, with a nonpainful lump at the nasal end of the left lower lid of one month's duration. Vision was unaffected, and his only complaint was the increasing swelling and redness of the lid. Examination revealed a tense, red, indurated swelling, about 2 by 3 cm., occupying the nasal two thirds of the left lower lid. The conjunctiva in the lower fornix was chemotic, and the mass had displaced the globe upward and temporally (fig. 3). Roentgenograms of the orbit showed only a localized area of increased density of soft tissues in the lower nasal aspect of the left orbit. Biopsy of the orbital mass was made because the infiltrative nature of the neoplasm



Fig. 3 (case 2).—Appearance of patient at the time of the initial examination.

rendered complete excision impossible. Nine days later, after the diagnosis of granular cell myoblastoma had been established, exenteration of the orbit was performed. This was followed by recurrence of a nodule along the lower orbital margin, for which radical excision, with skin grafting, was performed on June 26. The wounds healed, and the patient remained free from clinical evidence of recurrence until Sept. 12, 1945, when he returned, complaining of the rather rapid development of a lump at the angle of the jaw. A large, firm mass was present in the region of the submaxillary gland. The growth rapidly enlarged until Nov. 20, 1945, when a radical dissection of the structures in the submental and submaxillary triangles was done by Dr. John M. Hanford. Histologic examination showed the lymph nodes to be largely replaced with tumor tissue identical in character with the primary growth in the orbit. Another mass appeared in the left cheek within six weeks. This growth was thought to be inoperable; so roentgen therapy was given, with considerable regression in size of the nodules. Recurrences have since taken place, and the growth is invading the bones of the orbit and face. The patient, when last seen on May 29, 1947, showed signs of generalized metastasis.

The pathologic report, as submitted by Dr. A. Purdy Stout, follows: "Sections of the biopsy specimen from the original tumor were stained with hematoxylin and eosin and by Masson's trichrome method. They showed a tumor that was made up of masses of rounded and polygonal cells, of relatively large size and moderately well demarcated borders, although in many instances these were so ill defined that the cells appeared to coalesce. The characteristic of the cytoplasm was the presence of a large number of fine, moderately acidophilic granules. The

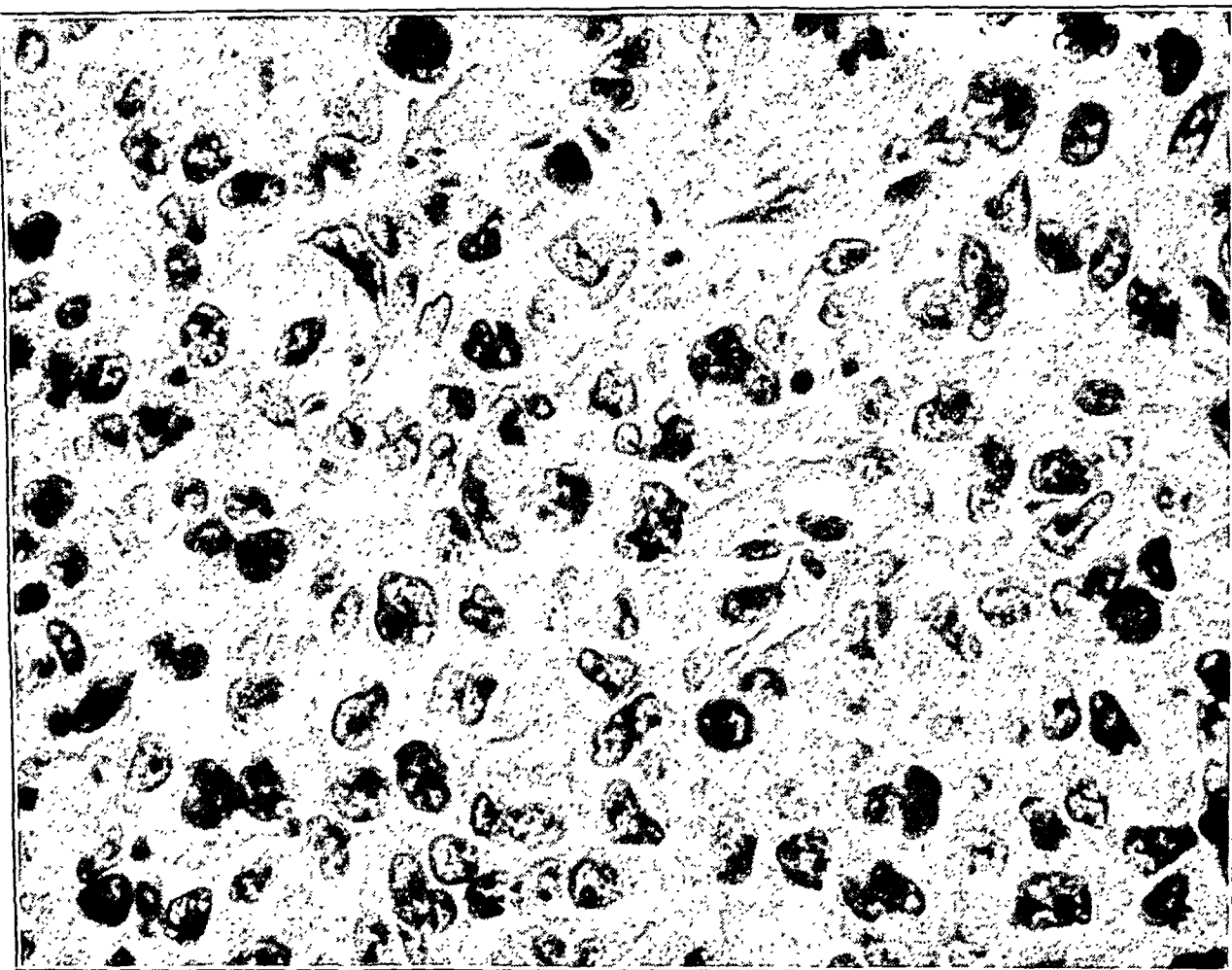


Fig. 4 (case 2).—Myoblastic cells, which are less embryonic than those in case 1. The cytoplasm is less granular and there is a tendency toward ribbon cells, but without striations. Hematoxylin and eosin stain; magnification,  $\times 750$ .

nuclei were moderately large and hyperchromatic and showed occasional mitoses. The cells had the characteristics of a malignant form of granular cell myoblastoma. Nowhere was the arrangement characteristic of the benign form (fig. 4).

"The mass in the orbit was large, measuring 29 by 28 mm. on the slide. The tumor pressed on the conjunctival sac, invaded one of the lids and was microscopically, although not grossly, invasive. The morphologic character both of the main tumor and of the recurrent nodule, removed after exenteration of the orbit, remained unchanged and was the same as that of the metastatic tumor in the lymph node.

"The diagnosis was that of granular cell myoblastoma of the orbit."

## SUMMARY

Granular cell myoblastoma is a relatively common tumor and widely distributed throughout the body. Since its occurrence in the orbit is rare, 2 cases are reported. The tumors in these cases presented no characteristic clinical picture, and the differential diagnosis was purely a histologic one. The tumor is more commonly benign, but in 1 of the present 2 cases it was malignant.

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# EXPERIMENTAL INVESTIGATION OF THE PATHOGENICITY OF DIPHATHEROIDS ISOLATED FROM THE HUMAN CONJUNCTIVA

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## GENERAL CONSIDERATIONS

*Bacteriologic Features of Diphtheroids.*—The first attempt to establish an etiologic relation between a diphtheroid and a disease of the eye dates back to 1879, when Italian investigators<sup>1</sup> isolated *Corynebacterium xerose* during the course of an institutional epidemic of xerophthalmia. Later, in 1883, German workers demonstrated the presence of diphtheroids on the conjunctiva of patients with a nutritional deficiency. However, it was soon realized that these bacteria are usually present on normal and inflamed conjunctivas, as well as on other normal and diseased surfaces of the body. It is of interest to note that in a recent review of the subject, published by the British Medical Research Council, the statement was made<sup>2</sup>:

It is very doubtful if *C. xerose* is even now sufficiently well characterized to deserve a specific rank. So authors present a picture formed from composite conceptions of various workers.

Likewise, the report of the Pickett-Thomson Research Laboratories<sup>3</sup>

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This study was aided by a grant from the Columbia Foundation.

Read at a meeting of the Society of American Bacteriologists, Philadelphia, May 13, 1947.

From the Laboratory for Ophthalmic Research, Mount Zion Hospital, San Francisco; the Department of Pathology, University of California School of Medicine, and the Laboratories of the Jewish Hospital, Philadelphia.

1. Andrews, F. W., and others: Diphtheria, Medical Research Council, London, His Majesty's Stationery Office, 1923, chap. 11, p. 370.

2. Hewlett, R. T., and Bulloch, W.: A System of Bacteriology in Relation to Medicine, Medical Research Council, no. 5, London, His Majesty's Stationery Office, 1930, chap. 3, p. 133.

3. Thomson, D., and Thomson, R.: The Classification and Identification of Certain Chromogenic Bacteria by Microphotography, Ann. Pickett-Thomson Research Lab. 2:51, 1925.

emphasized that the systematic study of the diphtheroids is still in a state of confusion, owing to the extreme variability in the morphologic and biochemical characteristics of these organisms.

In general, corynebacteria are described as nonmotile, gram-positive, aerobic, nonsporulating rods, resembling *Corynebacterium diphtheriae*, usually showing uneven staining and variable morphologic changes during growth. Young cultures (eight to twelve hours old) show solid forms only, but as they get older (twenty-four to forty-eight hours) the bacilli acquire elongated, pear-shaped forms, clubbing and barring. The fermentation of carbohydrates is variable.<sup>4</sup> Agglutination tests are difficult to perform because of spontaneous clumping. Identification by other serologic methods is likewise unsatisfactory, since complete studies have not been made of their antigenic structure.

The ophthalmologist who performs an iridectomy or an operation for cataract is interested to know whether or not diphtheroids, which are almost constantly present on the normal and inflamed conjunctiva, may exert serious injury when transferred by means of a surgical instrument to the interior of the eye. Axenfeld and his students<sup>5</sup> answered this question negatively over a generation ago. Nevertheless, it was deemed important to reinvestigate this problem in the light of the following new developments:

1. Many species of diphtheroids are now recognized as capable of producing disease.<sup>6</sup> Thus, a fatal human case of meningitis<sup>7</sup> and another of endocarditis<sup>8</sup> have been ascribed to corynebacteria. Likewise, cutaneous lesions in service men who had returned from the New Hebrides and the Mariana Islands of the Pacific were recently reported to be due to *Corynebacterium hemolyticum*.<sup>9</sup> With newer methods, specific toxins have been

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4. Barratt, M. M.: A Study of *Corynebacterium Diphtheriae* and Other Members of the Genus *Corynebacterium* with Special Reference to Fermentative Activity, *J. Hyg.* 23:241, 1924.

5. Axenfeld, T.: *Bacteriology of the Eye*, translated by A. MacNab, New York, William Wood & Company, 1908, pp. 196-198.

6. Bruce, E. A.: Ophthalmia in Sheep Caused by *Corynebacterium Enzymicum* and Its Transmission to Man, *Canad. J. Comp. Med.* 7:369, 1943. Cotchin, E.: *Corynebacterium Equi* in the Submaxillary Lymph Nodes of Swine, *J. Comp. Path. & Therap.* 53:298, 1943. Merchant, I. A.: A Study of the *Corynebacteria* Associated with Diseases of Domestic Animals, *J. Bact.* 30:95, 1935. Fraser, I. C.; Robson, J. M., and Scott, A. A. B.: Experimental Diphtheroid Infections of the Rabbit's Eye and Their Treatment, *Brit. J. Pharmacol.* 1:241, 1946.

7. Tesdal, M.: Fatal Meningitis Caused by a *Corynebacterium*, *Acta med. Scandinav.* 83:351, 1934.

8. Foord, A. G., and Stone, W. J.: Endocarditis Caused by Diphtheroid Bacillus, *Am. J. Clin. Path.* 4:492, 1934.

9. MacLean, P. D.; Liebow, A. A., and Rosenberg, A. A.: A Hemolytic *Corynebacterium* Resembling *Corynebacterium Ovis* and *Corynebacterium Pyogenes* in Man, *J. Infect. Dis.* 79:69, 1946.

demonstrated for *Corynebacterium pyogenes*,<sup>10</sup> the cause of abscesses in cattle and swine, and for *Corynebacterium ovis*,<sup>11</sup> which produces caseous and suppurative adenitis and pulmonary abscess in sheep and ulcerative lymphangitis in horses.

2. A number of micro-organisms, ordinarily nonpathogenic for animals, may acquire pathogenicity, while others become more virulent when inoculated in a medium of mucin.

We therefore undertook to demonstrate whether or not diphtheroids are pathogenic in special circumstances, as in the presence of mucin, and whether they can produce a soluble toxin.

*Properties of Mucin.*—Mucin, which is manufactured in the glands of the conjunctiva and other mucous membranes, is a protein conjugated with carbohydrate. Like gastric mucin, it contains, presumably, mucoitin-sulfuric acid.<sup>12</sup> When mucin is used as a vehicle in which to suspend certain bacteria, the organisms may acquire an increase in virulence for experimental animals. The mechanism is essentially as follows: Mucin functions as a protective capsule for the micro-organisms, permitting them to proliferate and survive in vivo. It also decreases phagocytosis and intracellular digestion of bacteria and reduces the bacteriolytic power of serums.<sup>13</sup> Thus far, this phenomenon has been demonstrated, among others, for meningococci,<sup>14</sup> pneumococci,<sup>13c</sup> typhoid bacilli,<sup>13f</sup> Hemoph-

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10. Lovell, R.: Studies on *Corynebacterium Pyogenes* with Special Reference to Toxin Production, *J. Path. & Bact.* **45**:339, 1937.

11. Petrie, G. F., and McClean, D.: The Inter-Relations of *Corynebacterium Ovis*, *Corynebacterium Diphtheriae* and Certain Diphtheroid Strains Derived from the Humas Nasopharynx, *J. Path. & Bact.* **39**:635, 1934.

12. Levene, P. A.: Hexosamines and Muco-Proteins, Monographs on Biochemistry, London, Longmans, Green & Co., 1925.

13. (a) McLeod, C.: The Mode of Action of Mucin in Experimental Meningococcus Infection, *Am. J. Hyg.* **34**:51, 1941. (b) Nungester, W. J., and Klepser, R. G.: A Possible Mechanism of Lowered Resistance to Pneumonia, *J. Bact.* **35**:32, 1938. (c) Nungester, W. J.; Jourdonais, L. F., and Wolf, A. A.: Effect of Mucin on Infections by Bacteria, *J. Infect. Dis.* **59**:11, 1936. (d) Tunnicliff, R.: Action of Gastric and Salivary Mucin on Phagocytosis, *ibid.* **66**:189, 1940. (e) Anderson, C. G., and Oag, R. K.: The Effect of Gastric Mucin on the Pathogenicity of the Meningococcus and Other Organisms, *Brit. J. Exper. Path.* **20**:25, 1939. (f) Rake, A.: Enhancement of Pathogenicity of Human Typhoid Organisms by Mucin, *Proc. Soc. Exper. Biol. & Med.* **32**:1523, 1935. (g) Mishulow, L.; Klein, I. F.; Liss, M. M., and Leifer, L.: Protection of Mice Against H. Pertussis by Serum, *J. Immunol.* **37**:17, 1939. (h) Griffiths, J. J.: The Use of Mucin in Experimental Infections of Mice with *Vibrio Cholerae*, *Pub. Health Rep.* **57**:707, 1942. (i) Olitski, L.: Mucin as a Resistance Lowering Substance, *Bact. Rev.* **12**:149, 1948.

14. McLeod.<sup>13a</sup> Nungester and Klepser.<sup>13b</sup> Nungester and others.<sup>13c</sup> Tunnicliff.<sup>13d</sup> Anderson and Oag.<sup>13e</sup>

ilus pertussis,<sup>13g</sup> *Vibrio cholerae*<sup>13h</sup> and the virus of influenza.<sup>15</sup> Since mucus (containing mucin) is increased in amount during the course of conjunctivitis when diphtheroids also increase in number, it seemed worth while to investigate the effects of mucin on diphtheroids which had been isolated from the human conjunctiva.

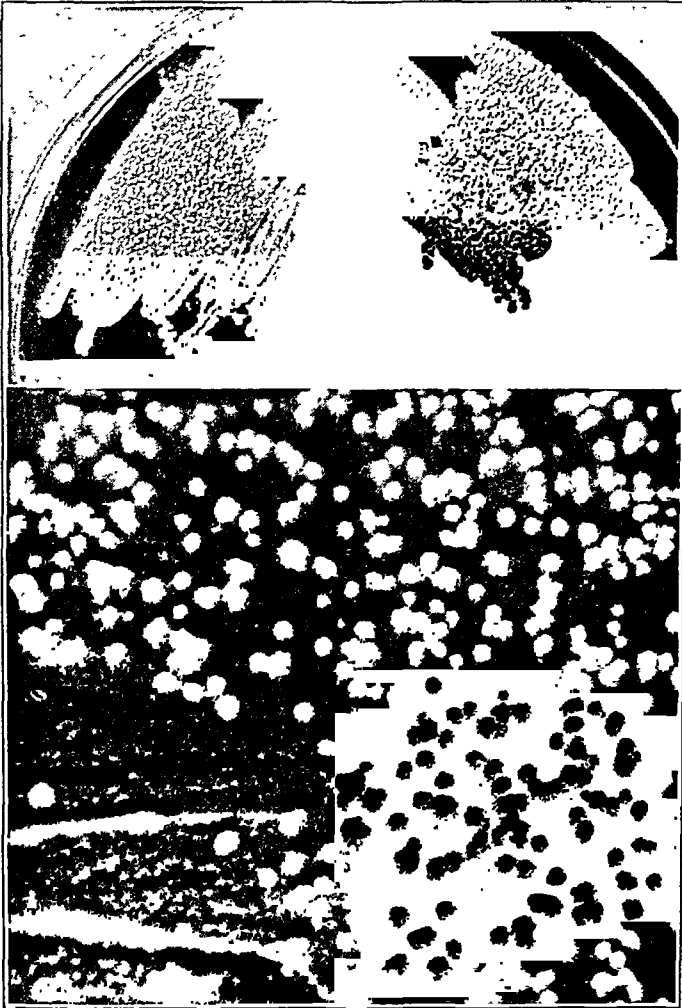


Fig. 1.—Dissociation in cultures of diphtheroids. Background shows original growth; surface colonies are mucoid variants (shown magnified in lower portion).

#### METHODS OF INVESTIGATION

*Cultural Studies.*—The cultures employed were isolated from normal human conjunctivas on plates of proteose 3 agar containing rabbit blood. The colonies when first appearing were minute, resembling dew drops. When forty-eight hours old they were small and transparent, with a

15. Wheeler, A. H., and Nungester, W. J.: Effect of Mucin on Influenza Virus Infection in Hamsters, *Science* 96:2482, 1942.

slight opacity in the center. Fermentation of dextrose and levulose was usually observed after seven days. Sucrose, maltose and galactose were not hydrolyzed. Dissociation (variation), as might be expected, was noted when the medium was changed to one containing dextrose. The colonies now appeared larger, more opaque, creamy and mucoid (fig. 1). Gram-positive rods were present, as usual; but coccoid forms were also seen. These variants attacked dextrose, maltose and levulose slowly (twenty-one days). Pigmented (orange-yellow) colonies were also observed.<sup>16</sup> These bacteria did not ferment any of the carbohydrates here listed. By careful selection of smooth colonies, we attempted to maintain the stability of the strain used in the experimental studies.

In addition to the usual V, Y, and club forms, the variants often showed in Gram preparations coccobacillary rods, which resembled chains of streptococci. At first suspected of being contaminants, they were repeatedly replated and studied by means of dark field illumination and in hanging drop preparations, where they were recognized as tiny coccobacilli.

*Technic of Inoculation.*—After a demonstration by Dr. Michael Hogan, of the department of ophthalmology, University of California, we performed several preliminary experiments in order to acquire skill in the technic of injection into the anterior chamber of albino rabbit eyes without injuring the iris.<sup>17</sup> The animals were anesthetized by an intravenous injection of pentobarbital sodium U.S.P. in a dose of 0.44 cc. per kilogram of body weight. The conjunctiva and cornea were cocaineized, after irrigation with a solution of benzalkonium chloride U.S.P. ("zephiran chloride"), 1:2,000. Diphtheroids were grown for twenty-four hours on proteose 3 agar, washed off with saline solution and immediately diluted and shaken to break up clumps. Standardized suspensions were prepared in mucin and in saline solution and plated to determine the viable count, as described later.

*Production of Toxin by Diphtheroids.*—A variety of methods was employed in an effort to demonstrate the production of toxin by diphtheroids. Among these were the Dolman<sup>18</sup> technic for staphylococcus toxin and Wadsworth medium II for production of toxin by diphtheria

16. Rother, W.: Ueber Farbstoffbildung bei zwei Xerosestämmen, *Centralbl. f. Bakt.* (Abt. 1) 90:127, 1923.

17. Herrenschwand, F.: Die pathogenen Mikroorganismen des Auges, Berlin, Urban & Schwarzenberg, 1927, p. 296. Benjamin, J., Jr.; Belt, E., and Krichesky, B.: Total Prostatectomy in the Rabbit and Intra-Ocular Transplantation of Prostatic Tissue, *J. Urol.* 44:109, 1940. Gilbert, W., and Plaut, F.: Ueber Kammerwasseruntersuchung, *Arch. f. Augenh.* 90:1, 1921.

18. Dolman, C. E.: Pathogenic and Antigenic Properties of Staphylococcus Toxin, *Canad. Pub. Health J.* 23:125, 1932.



bacilli.<sup>19</sup> When these failed, we turned to the newly developed synthetic medium of Mueller and Miller<sup>20</sup> and Pappenheimer and Johnson.<sup>21</sup> The formula selected, 10 per cent casein hydrolysate with dextrose in place of maltose, 0.1 per cent agar and 0.3 microgram of ferrous sulfate per cubic centimeter, gave profuse growth of diphtheroids. After eight days' cultivation, Seitz filtrates were prepared and tested for hemolytic activity, dermonecrosis and capacity to injure the deeper tissues of the rabbit eye. They were stored at  $-77^{\circ}\text{C}$ . in a carbon dioxide snow refrigerator until used.

#### EXPERIMENTAL RESULTS

*Studies in Vitro.*—Before investigating the effects of mucin on the pathogenicity of diphtheroids, we determined whether or not the substance supports their growth in vitro. Granular mucin<sup>22</sup> was suspended in buffered saline solution, according to the method of Rake,<sup>23</sup> and clarified by centrifugation. After several samples were tested for viscosity, lot 3111, in a final concentration of 3 per cent, was found suitable.

A forty-eight hour old culture was washed off from proteose 3 agar and diluted in one series with buffered saline solution and in another with buffered mucin solution. The bacterial suspensions were incubated at  $37^{\circ}\text{C}$ . and shaken thoroughly with beads in a Kahn shaking machine to break up clumps. At frequent intervals during a period of twenty-four hours, samples were removed, diluted and again shaken. Aliquots of 0.05 cc. were plated on proteose 3 agar in order to determine the total number of viable bacteria. These tests were performed in triplicate, and crowding of colonies was avoided.<sup>24</sup> The logarithms of the number of viable bacteria were plotted against time (in hours) on semilogarithmic paper and the growth curves compared.

As seen in figure 2, when the diphtheroids were cultivated in a medium of mucin, their growth curve shows an initial stationary phase, a lag phase, a logarithmic phase, a phase of negative acceleration and a

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19. Wadsworth, A. B., and Wheeler, M. W.: Toxigenesis of Diphtheria Bacillus, *J. Infect. Dis.* **55**:123, 1933.

20. Mueller, J. H., and Miller, P. A.: Production of Diphtheric Toxin of High Potency (100 IF) on a Reproducible Medium, *J. Immunol.* **40**:21, 1941. Mueller, J. H.: The Influence of Iron on the Production of Diphtheria Toxin, *ibid.* **42**:343, 1941.

21. Pappenheimer, A. M., Jr., and Johnson, S. J.: Studies in Diphtheria Toxin Production: III. A Simple Gelatin Hydrolysate Medium and Some Properties of the Toxin Produced Thereon, *Brit. J. Exper. Path.* **18**:239, 1937

22. The mucin, 1701, was prepared by the Wilson Laboratories, Chicago.

23. Rake, G.: The Mouse Protection Test in the Standardization of Anti-Meningococcus Serum, *Canad. Pub. Health J.* **28**:265, 1937.

24. Wilson, G. S.: The Proportion of Viable Bacteria in Young Cultures with Especial Reference to the Technique Employed in Counting, *J. Bact.* **7**:405, 1922.

maximum stationary phase, thus resembling a standard bacterial growth curve.<sup>25</sup> Hence, mucin is a suitable medium for the growth of diphtheroids. Buffered saline solution, on the other hand, is not suitable, as shown by a decreasing bacterial population from hour to hour.

*Studies in Vivo.*—Suspensions of diphtheroids in mucin cause a much earlier, more intense and more enduring inflammatory reaction than similar doses made up in saline solution. Thus, when several million bacilli

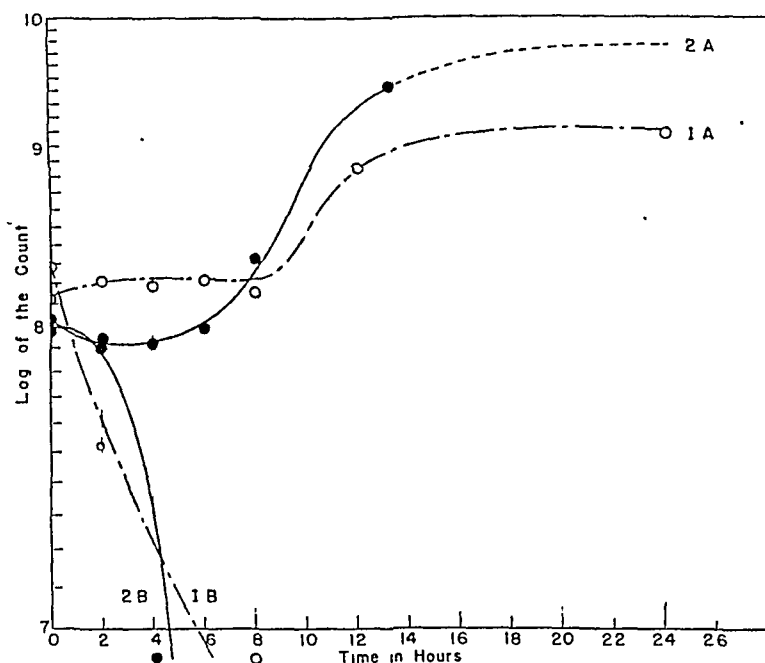


Fig. 2.—Growth curves for diphtheroids: Curves 1A and 2A represent results of two separate experiments performed with bacilli suspended in mucin; curves 1B and 2B, results of analogous experiments with diphtheroids suspended in saline solution.

were injected in a menstuum of saline solution into the anterior chamber of albino rabbit eyes, there was little cytologic reaction, and few bacteria were seen in the aqueous humor, which was removed at varying intervals up to three days and stained by means of supravital staining and the Giemsa and Gram stains. With similar doses of bacteria suspended in mucin, there was, after a lag of about ten hours, a prolific exudate, consisting largely of neutrophils (70 to 90 per cent) and a varying number of lymphocytes and histiocytes. Diphtheroids were also much more numerous. After two to three days, both cells and bacteria began to decrease in number. Similar experiments were performed in the abdominal cavity of mice, where the phenomenon could be studied with greater facility. It was clearly demonstrated that mucin favors the multiplication and survival of the stain of diphtheroids under investigation.

25. Buchanan, E. R.: Growth Curves of Bacteria, in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunity, Chicago, University of Chicago Press, 1928, p. 46.

TABLE 1.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 100,000 Viable Bacilli) Into Anterior Chamber of Albino Rabbits\**

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
Series E: Living Culture Suspended in Mucin			
48	R	Intense congestion of lower edge of ciliary body and ora; cornea clear	Congestion and polymorphonuclear cell exudate at corneoscleral junction; scant purulent exudate in anterior chamber
49	R	Opacity of cornea and lens; pupil dilated; limbus and ciliary body engorged	Large recent organizing hemorrhage at one corneoscleral junction; polymorphonuclear cell exudate in filtration angle and anterior chamber
50	R	Cornea hazy; ora slightly congested	Fibroblastic proliferation at both corneoscleral junctions; old polymorphonuclear cell exudate; swelling of endothelial cells and macrophages; reaction extending into base of ciliary body; proliferation of corneal and ciliary epithelium
29	R	Cornea wrinkled and hazy; irregular projections from iris into pupillary area; engorgement of ciliary body	Small amount of recent hemorrhage at one corneoscleral junction; veins and lymphatics dilated; eosinophilic exudate; vessels dilated at opposite angle
30	R	Small opacity at edge of iris; slight opacity near lower area of limbus; ora slightly congested	One corneoscleral angle normal except for slight dilation of vessels; at other, cornea greatly thickened by edema and a considerable eosinophilic exudate; vessels dilated
31	R	Pupil large; cornea wrinkled and slightly hazy; opaque spot in pupillary area; ora congested; small opacity on lens	At one corneoscleral angle and, to less extent, in opposite angle, dilatation of vessels and slight polymorphonuclear cell and lymphocytic exudate; at angle of anterior chamber and iris on most involved site of cornea, purulent exudate with edema of iris
Series F: Living Culture Suspended in Saline Solution			
29	L	Cornea slightly hazy; ciliary body congested	Occasional eosinophilic polymorphonuclear leukocyte in undilated vessels; moderate congestion of some ciliary processes
30	L	Cornea clear; corona engorged at inner edge	Normal
31	L	Pupil large; cornea clear; corona slightly congested	Ciliary bodies irregularly congested
49	L	Cornea clear; pupil large; congestion of ora	Small hemorrhage in one fold of ciliary process
48	L	Cornea clear; pupil small; slight congestion of lower edge of ciliary body	Congestion and pyknotic nuclei at one corneoscleral junction
50	L	Cornea clear; pupil normal; slight congestion of ora; one large, heavily engorged area of retina at lower edge of ora	Edema, necrosis and a little corneal epithelial proliferation at one spot

Smaller doses, 100,000 to 200,000 bacilli, were employed in a detailed clinical and pathologic study of the pathogenicity of diphtheroids. Heat-killed suspensions of bacteria and control doses of mucin alone were similarly inoculated into the anterior chamber of albino rabbit eyes in a volume of 0.1 cc. In this way, the foreign protein factor and the effects of mucin per se could be evaluated. In tables 1 to 3 are presented

TABLE 1.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 100,000 Viable Bacilli) Into Anterior Chamber of Albino Rabbits\*—(Continued)*

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
Series G: Killed Bacteria Suspended in Mucin			
54	R	Cornea clear; pupil normal; ora congested	Edema at periphery of corneoscleral junction on both sides; congestion and recent hemorrhage; polymorphonuclear cell exudate; old fibroblasts, macrophages and lymphocytes from corona into ciliary body
55	R	Cornea clear; pupil normal; ora heavily engorged	Normal
56	R	Cornea clear; pupil small; slight congestion of ora	Collection of fibroblasts and degenerating polymorphonuclear cell at one corneoscleral junction and barely perceptible at the other
32	R	Normal	Small area limited to cornea at corneoscleral angle, which is infiltrated with polymorphonuclear cells and lymphocytes; irregular congestion and edema of ciliary folds
32	L	Normal	Reaction similar to that in right eye of rabbit 32
Series H: Killed Bacteria Suspended in Saline Solution			
54	L	Cornea clear; pupil large; slight congestion of ora	Tiny area of necrosis and fibroblastic proliferation, apparently needle tract
55	L	Cornea clear; pupil large; opacity at periphery of lens; ora heavily engorged	Small collection of fibroblasts and old polymorphonuclear leukocytes at corneoscleral junction
56	L	Cornea clear; pupil small; heavy engorgement of cornea	Ciliary processes moderately congested

\*Observations were made at the end of forty-eight hours.

extracts from daily protocols, as well as results of histologic examinations made after enucleation of the animals' eyes. It will be seen (figs. 3 and 4) that, whereas mild inflammation of the cornea and uveal tract occurs as the result of intraocular injection with diphtheroids suspended in saline solution, the reaction is much severer and lasts much longer when a menstruum of mucin is used. Mucin also increases the irritant

action of killed bacilli. This is noteworthy, since when injected alone into the anterior chamber it is virtually innocuous.

TABLE 2.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 105,000 Viable Bacilli) Into Albino Rabbits\**

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
		Series A: Living Culture Suspended in Mucin	
52	R	Cornea wrinkled, protruding and opaque; circumcorneal vessels engorged; pupil very large; ora congested	At both edges of cornea, extensive congestion, hemorrhage and polymorphonuclear exudate; fibroblastic proliferation, macrophages and edema; reaction extends to base of ciliary body
51	R	Cornea clear, wrinkled at edge of limbus; long, thin opacity in midline; hypopyon at lower edge of cornea; congestion of vessels; engorgement of ora and iris; detachment and heavy engorgement of retina; pupil large	Section unsatisfactory
53	R	Cornea thickened and wrinkled, with opacity in midline; congestion of circumcorneal vessels; ora extremely congested and heavily engorged; two areas of discoloration on retina	Similar to reaction in right eye of rabbit 52
		Series B: Living Culture Suspended in Saline Solution	
51	L	Cornea slightly hazy; pupil normal; engorgement of ora	Normal
52	L	Cornea clear; pupil large; slight congestion of ora	Slight focal edema and necrosis and endothelial swelling at periphery of cornea
53	L	Cornea clear; pupil small; ora congested	Practically normal; focal edema in sclera at corneoscleral junction
		Series C: Killed Bacteria Suspended in Mucin	
59	R	Cornea clear; slight congestion of ora; area of discoloration of retina at lower edge of ora	Recent small hemorrhage into ciliary processes; one corneoscleral junction showing barely perceptible focus of a few degenerated polymorphonuclear cells and fibroblasts; apparently needle tract
57	R	Cornea clear; slight congestion of ora; two small areas of congestion at lower edge of ora on retina	At one corneoscleral junction, small collection of lymphocytes; on opposite side, recent hemorrhage in ciliary process
58	R	Cornea clear; pupil normal; slight congestion of ora; two areas of congestion on retina	At corneoscleral junction, lymphocytes and fibroblasts, extending into ciliary body; vessels dilated; recent hemorrhage into ciliary process

The ocular lesions which were produced by diphtheroids usually progressed spontaneously during the course of two to three weeks.

It must be emphasized that the pathogenicity of diphtheroids was demonstrable only when the interior of the albino rabbit eyes was used as the test medium. No untoward effects were observed after subconjunctival or intradermal injection into rabbits or after intracerebral or intra-abdominal inoculation of mice. Absence of invasive power was

TABLE 2.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 105,000 Viable Bacilli) Into Albino Rabbits\**  
—(Continued)

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
Series D: Killed Bacteria Suspended in Saline Solution			
57	L	Cornea clear; three small areas of discoloration on retina	Small, dense collection of lymphocytes and fibroblasts at both corneoscleral junctions
58	L	Cornea clear; ora engorged	Small hemorrhage into ciliary process at opposite corneoscleral junction
59	L	Cornea clear; pupil very large; ora congested; slight discoloration at edge of ora on retina	Normal
Series E: Mucin Only			
33	R	Bleb at corneoscleral angle	One side of ciliary body congested and small organized scar at iris
40	L	Normal	Small collection of lymphocytes in sclera of anterior part of eye
356	R	Normal	Small, recently organized scar at posterior surface of cornea at periphery
357	R	Normal	Recently organized scar of cornea
Series F: Saline Solution Only			
		Ten animals given injections; all normal	normal

\*Observations were made at the end of seventy-two hours.

established by Menkin's<sup>26</sup> technic. Large doses (10,000,000 bacilli) were suspended in mucin and in saline solution and injected intracutaneously into the foreleg of rabbits. Twenty-four hours later the axillary lymph nodes, spleen, liver and heart's blood were cultured, but no diphtheroids could be isolated.

26. Menkin, V.: Invasiveness and Virulence in Relation to Resistance, J. Infect. Dis. 58:81, 1936.

TABLE 3.—*Clinical Observations After Injection of Diphtheroids (Dose, 200,000 Bacilli) Into Anterior Chamber of Albino Rabbits\**

Rabbit No.	Eye	Living Culture in Mucin	Rabbit No.	Eye	Killed Culture in Mucin
337	R	Cornea milky, opaque; iris invisible; chemosis of cornea; crusting of lids; scleral vessels congested; circumcorneal red band; lower palpebral conjunctiva more congested than upper, which is only slightly so	337	L	Circumcorneal vessels slightly congested; irregular inner margin of iris with fibrinous exudate; striae of iris slightly pink
338	R	Conjunctiva congested, lids red, cornea slightly cloudy; no reaction to light; hypopyon, fibrinous exudate, iris markings cannot be seen	338	L	Normal, except slight irregularity of inner margin of iris at one point
349	R	Lids red, moist, swollen; crusty, with slight discharge; conjunctival sclera and circumcorneal vessels congested; pupils reactive to light; cornea faintly cloudy, iris markings broadened into red bands	349	L	Normal
340	R	Lids slightly pink with slight discharge; palpebral conjunctiva slightly congested, chemosis of cornea, circumcorneal vessels forming tortuous reddish band; severe iritis; irregular margin and fibrinous exudate at one point remaining	340	L	Normal, except for slight irregularity of inner margin of iris at point of inoculation
341	R	Pronounced exophthalmos; cornea chemotic; lids slightly crusty with slight white, mucoid discharge; no reaction to light; conjunctiva normal; congestion of circumcorneal vessels to form band; scleral vessels not noticeable; cornea faintly cloudy; very severe iritis	341	L	Normal
342	R	Lids crusty with slight opaque, white discharge in conjunctiva; chemosis and haziness of cornea intense; hypopyon; circumcorneal vessels congested, forming bright red band	342	L	Cornea faintly cloudy; iris markings red; circumcorneal vessels and lower conjunctiva congested
		Living Culture in Saline Solution			Killed Culture in Saline Culture
343	R	Exophthalmos and chemosis of cornea pronounced; mucoid discharge from conjunctiva; photophobia; no reaction to light; lids red and slightly edematous; conjunctival vessels congested; scleral and circumcorneal vessels congested; cornea milky and opaque	343	L	Normal
344	R	Iritis; enlargement of striae; some broad, others less so, but considerable increase; reacts to light slowly; fibrinous exudate	344	L	Normal
345	R	Very mild iritis	345	L	Normal
346	R	Very mild iritis	346	L	Normal
347	R	Slight iritis	347	L	Normal
		Mucin (Control)			Saline Solution (Control)
355	R	Normal	355	L	Normal
356	R	Normal	356	L	Normal
357	R	Normal	357	L	Normal

\*Observations were made after six days.

Suspensions of diphtheroids, made up in saline solution or mucin, were also instilled into the nostrils of mice which had been lightly anesthetized with ether. These bacteria could not be recovered from any of the viscera or the heart's blood twenty-four hours later.



Fig. 3A (rabbit 52).—Histologic section of left eye obtained seventy-two hours after injection of diphtheroids (suspended in saline solution) into anterior chamber. There are slight focal edema and necrosis and endothelial swelling at the periphery of the cornea.

#### DEMONSTRATION OF TOXIC FILTRATES IN CULTURES OF DIPHTHEROIDS

Sterile filtrates which were prepared by the Pappenheimer and Johnson method<sup>21</sup> were inoculated into the anterior chamber of 9 anesthetized albino rabbits. As seen in the protocols cited here, the filtrates produced moderately severe inflammation of the iris and cornea in 7 of the animals. These lesions cleared in a week or two. Filtrates which had been boiled for ten minutes were harmless.



These filtrates were not hemolytic for rabbit, sheep or human erythrocytes. No signs of necrosis were demonstrable after intracutaneous or subconjunctival injection into rabbits or guinea pigs. Likewise, intraven-

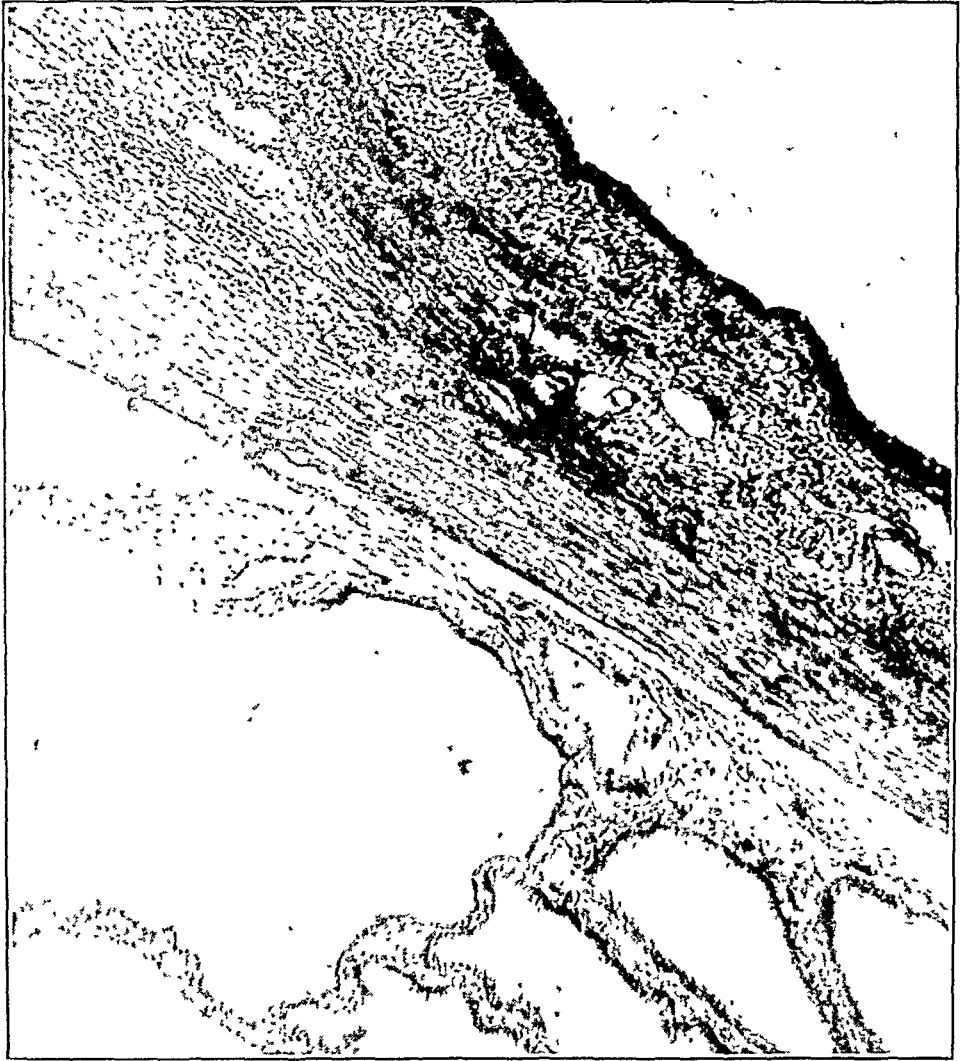


Fig. 3B.—Right eye, after a similar injection of diphtheroids suspended in mucin solution. There are extensive congestion, hemorrhage and a polymorphonuclear cell exudate at both edges of the cornea, as well as fibroblastic proliferation and edema. The reaction extends to the base of the ciliary body. (Zeiss ocular;  $\times 120$ ).

ous injection into these animals and intracerebral or intra-abdominal inoculation of white mice were without effect.

PROTOCOL.—Filtrate 129 AB, 0.1 cc., injected March 9, 1944 with the animal under pentobarbital anesthesia.

RABBIT 7A.—Twenty-four Hours After Injection: Eye closed; slight opacity of cornea; markings of iris not visible; plastic exudate at inner edge of iris.

Seventy-Two Hours: Band composed of bright red blood vessels at limbus and congestion of palpebral conjunctiva.

Five Days: Eye essentially normal.

RABBIT 79.—Twenty-Four Hours: Circumcorneal vessels congested, forming bright red band at limbus; vessels of bulbar conjunctiva also congested; slight iritis.

Seventy-Two Hours: Iritis persists (disappeared three days later).

RABBIT 80.—Twenty-Four Hours: Plastic iritis; congestion of palpebral vessels; episcleritis.

Seventy-Two Hours: Congestion of palpebral conjunctiva and circumcorneal vessels; mild iritis.

Six Days: Eye normal.

RABBIT 82.—Forty-Four Hours: Cornea, the color of mother of pearl; congestion of circumcorneal and palpebral vessels.

Five Days: Corneal opacity persisting; suggestion of keratoconus.

Eight Days: Eye clearing.

PROTOCOL 2.—Filtrate 130, prepared April 5, 1944; injected May 1, 1944 with animal under pentobarbital anesthesia; dose, 0.1 cc.

RABBIT 7B.—Three Days After Injection: Lids edematous; circumcorneal vessels red; intense opacity of cornea; iris obliterated; pupil not reactive to light.

Seven Days: Three quarters of cornea opaque; iris barely seen; pupil not reactive to light; edema of nictitating membrane; beginning of pannus.

RABBIT 10.—Three Days: Lids and conjunctiva inflamed; exophthalmos; cornea opaque; loss of light reflex; iris markings obliterated.

Seven Days: Cornea opaque; pannus progressing; lid margins red; pupillary reaction to light sluggish.

RABBIT 11.—Three Days: Eye protruding; cornea opaque; loss of pupillary reflex.

Seven Days: Cornea showing milky, white opacity and resembling keratoconus; iris markings not seen.

#### COMMENT AND SUMMARY

Diphtheroids, resembling *C. xerose*, which were isolated from the human conjunctiva, grew well in a menstruum of mucin. Similarly, when suspended in this medium and inoculated into the anterior chamber of the eyes of albino rabbits, cultures retained their viability *in vivo* for several days, while in suspensions in saline solution they were rapidly destroyed.

Intraocular injection of diphtheroids suspended in saline solution into albino rabbits produced moderate inflammation of the ciliary process. When suspended in mucin, the reaction lasted longer, was much severer and was associated with acute keratitis. The lesions usually regressed spontaneously within two or three weeks.

While suspensions of killed cultures of diphtheroids in saline solution produced mild inflammatory changes in the ciliary process, which

were seen in histologic sections, none was visible grossly. Suspensions in mucin produced severer inflammatory reactions. Since mucin by itself is relatively innocuous, it is suggested on the basis of these studies, and those of others,<sup>27</sup> that it protects bacteria from the digestive actions of humoral and cellular proteolytic enzymes and other immunologic defense mechanisms. Living diphtheroids are thus permitted to grow and exert their pathogenic activity.

By applying the recently developed methods of Mueller and Miller and Pappenheimer and Johnson, it was possible to demonstrate that a filtrate which is produced by growing diphtheroids in a medium of very low iron concentration is injurious to the uvea and cornea, but not to the skin or conjunctiva of albino rabbits.

On the basis of these investigations, it may be concluded that diphtheroids which are almost constantly present on the normal and inflamed human conjunctiva may be considered as potential pathogens, which may exert injury when they are introduced into the interior of the eye.

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27. Komarov, S. A.: The Influence of Mucoitinsulfuric Acid on Peptic Digestion, *Am. J. Digest. Dis.* 3:164, 1936. Miller, C. P.: A Study of Experimental Meningococcus Infection, *Proc. Soc. Exper. Biol. & Med.* 32:1136, 1935.

## CONTAMINATED OPHTHALMIC OINTMENTS

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PHILADELPHIA

OPHTHALMIC OINTMENTS have been, and are, prescribed and used by ocular surgeons throughout the civilized world. By far the most commonly used by the family physician is yellow mercuric oxide. The American lay public long used this ointment as a household remedy for external diseases of the eye; it is now to be replaced by sulfathiazole ointment. In the experience of one of us (L. L.), the same collapsible tube containing an ointment of mercury bichloride U.S.P., boric acid ointment U.S.P. or ammoniated mercury ointment U.S.P. has been used in the treatment of numerous patients in office practice, with a thought to economy, until the last wormy drip has been expressed. At the Wills Hospital, it was our experience for years to use an ointment containing mercury bichloride (1:3,000) after all cataract operations, merely because we had seen our predecessors use the same technic. Not more than seven years ago, we witnessed a corneal transplantation by a well known surgeon of New York in which he squeezed a goodly portion of an ointment from a collapsible tube into the patient's eye for antiseptis and lubrication. On another occasion, we saw motion pictures of a transplantation performed by the same surgeon in which he advocated the use of sulfathiazole, 5 per cent, immediately after the operation and then, at a later period, penicillin ointment.

Most ophthalmic surgeons and students of ophthalmology are inclined to play "follow the leader." It is not good form to question the masters who have obtained good results. But personal experience with a succession of infections following operations makes the surgeon stop to recount his steps in an effort to discover the missing link in asepsis and antisepsis. Our attention was directed to the use of ointments in general. Dismissing at once the old ointment jar, we directed our study toward the sterility and the maintenance of sterility of ointments commonly used in

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Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, April 24, 1947.

collapsible tubes. It is our experience that the first sample of the ointment expressed from a fresh tube, regardless of the name of the ointment, differed in color and consistency from the second. It was also found that the nozzle of the tube was never free from ointment after a quantity had been expressed. Pressure by the fingers seemed to leave a wormlike protrusion at the tip of the tube, over which the cap was replaced. This overflowing quantity of ointment remained in the cap and on the nozzle of the tube until the next use. Not always is it customary to express a quantity on a towel or a pledget of cotton before the second toothpaste-like ribbon is inserted into the eye. In other words, the ophthalmologist has a false sense of security that the ointment in every collapsible tube is sterile until the last bit is squeezed out. It has been the belief that the contents of the tube of ophthalmic ointment were sterile at the beginning and at the end. I feel certain that most ophthalmologists have used these ointments in the treatment of corneal ulcers with the belief that the germicidal value of its contents was sufficient to destroy the bacteria present.

Strangely, we ophthalmologists have never seen a collapsible tube of ophthalmic ointment marked "sterile;" yet for years we have ordered such ointments in the treatment of hordeolum, blepharitis marginalis, ulcerative keratitis and injuries to the eye, with a smugness founded on custom rather than on scientific knowledge, in the belief that healing qualities of ointments were guaranteed by every textbook on ophthalmology. Fisher, Accousti and Thompson<sup>1</sup> reported from the Warner Institute for Therapeutic Research that ointments containing 5 per cent sulfanilamide, sulfathiazole or sulfadiazine in a water-dispersible base may become contaminated with disease-producing organisms which these sulfonamide compounds are not capable of killing.

#### PRESENT INVESTIGATION

We wish to present evidence that most ophthalmic ointments in new and unused tubes are sterile. We wish to prove that once a fresh tube is opened the remaining contents are frequently contaminated.

*Culture Mediums.*—The culture medium used in this experiment was brain-heart infusion agar with sterile human blood. Approximately 1 inch (2.5 cm.) of sample was expressed from each collapsible tube on to the culture medium. The period of incubation varied from one week to ten days. The first culture appeared within forty-eight to seventy-two hours. The incubation temperature was 37 C. The ophthalmic ointments used in this series of experiments were obtained from six manufacturers.

*Ointments Cultured.*—Cultures were made of the contents of 50 used tubes and 24 unused tubes of commonly known ophthalmic ointments as found on the

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1. Fisher, C. V.; Accousti, N. J., and Thompson, M. R.: Bacterial Contaminations in Sulfonamide Ointments, J. A. M. A. 122:855-858 (July 24) 1943.

open market. Three control Petri dishes were also observed, the mediums having been exposed for the same length of time as that required to inoculate the mediums.

**Used Tube Cultures:** Of the 50 tubes which had been used more than once, a goodly proportion showed contamination with bacteria, such as *Staphylococcus albus hemolyticus*, *Staphylococcus aureus hemolyticus*, fungi (species not determined) and other organisms which were not identifiable by microscopic examination alone.

Of 15 tubes of 5 per cent sulfathiazole ointment which had been used at least once, 8 yielded growth. Of 11 tubes of an ointment containing mercury bichloride (1:3,000), 4 were contaminated. Of 5 tubes of penicillin ointment (500 units per gram), 2 samples yielded growth. Of 7 tubes containing epinephrine bitartrate which had been opened once or more, 2 yielded pathogenic organisms. One of 6 tubes of atropine sulfate ointment which had been used yielded growth. Three tubes of ointment containing tetracaine hydrochloride were found to be sterile. A tube of ointment containing physostigmine salicylate, 1 per cent, which had been used for patients postoperatively showed many fungi. One borofax<sup>R</sup> tube<sup>2</sup> was sterile.

**Unused Tube Cultures:** Twenty-four new tubes of ointment were selected from a stock pile of boxes containing 5 per cent sulfathiazole ointment. One tube was selected from each supply box as a spot check, each box having 50 small tubes of 1/8 ounce (3.8 Gm.) each.

In 12 new, unused tubes the first portion of ointment was cultured; no sample yielded growth. In another group of 12 new tubes, the entire contents of each tube was cultured; that of 1 tube contained organisms. Three controls, consisting of blood agar, were exposed for the same length of time as that required to smear the ointment from the tube. The three controls were sterile on culture, indicating there was no contamination from the outside atmosphere during the period of exposure.

*Comment.*—There was sufficient evidence from all the experiments to indicate that the unused tube of ointment was in most instances sterile, whereas the used tubes were frequently contaminated.

The observations in this study call for a revaluation of the use of ophthalmic ointments in the eye after operation and of the use of ointments for ophthalmic conditions in general.

We appreciate the difficulty of sterilizing ophthalmic ointments. The composition of the tubes and that of the ointments enter into the difficulty of marketing or preparing sterile ointments in collapsible tubes.

#### CONCLUSIONS

We have no proof that infections actually occur from the use of contaminated ointments. Surgeons of experience, however, do not wish to

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2. Borofax contains 10 per cent boric acid in an ointment base.

publicize overwhelming evidence in the form of blind eyes. We do not have proof that the organisms found in the contamination were pathogenic bacteria. The mere fact that the ointments contain organisms is sufficient proof that pathogenic bacteria may also be present. One may question why more infections do not occur from the use of ointment in used tubes. The answer can be only a conjecture. Either the lysozymes of the tears have their effect on certain bacteria or the eye itself possesses a factor, *X*, which saves most patients from infection following intra-ocular operation. Scientists do not willingly or knowingly place contaminated ointments into open wounds, not even into a healthy eye.

Our experiments have led us to discontinue the postoperative use of ointments. We get along very well without them. Perhaps we, too, were formerly the subjects of habit and custom.

We were greatly surprised to learn that sulfathiazole ointment and penicillin ointment may become contaminated before the contents of the tube are exhausted. We have lost faith in the use of ointments. Our confidence can be restored only if an ointment could be produced sterile in containers for one application only. It is hoped that the experiments here reported may stimulate renewed interest in ophthalmic therapeutics.

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#### DISCUSSION

DR. LOUIS GERSHENFELD, Philadelphia: We are indebted to Dr. Lehrfeld and Dr. Donnelly for the presentation of this paper on the sterility of ointments. In general, information like this comes from laboratory workers, and perhaps does not attract the attention of the rank and file of physicians. It certainly does not reach the ophthalmologist with the same impressiveness and significance as it does when coming from the ophthalmic surgeon. This paper should arouse interest.

I recall distinctly that about twenty-five years ago I was much concerned about the sterility of ampules, in particular those used for internal medication. It happened that I was at a meeting with the Commissioner of Food and Drugs. As you know, the Food and Drug Administration is interested primarily in the traffic of food and drugs as it is concerned with interstate commerce. During the discussion I asked Mr. Campbell, the commissioner, whether the members of his department had examined ampules on the open market. He did not recall at the time and turned to two of his assistants. They replied that they did not think so. I then said, "Don't you think it would be of more interest, and certainly of greater value, if one were concerned with the examination of ampules on the market, especially the sterility of solutions for parenteral injection, than with routine matters, such as whether the strychnine content of *nux vomica* is 1.15 or 1.05 per cent?" The latter is important, but it is of greater importance to be sure that solutions which are injected directly into the system, and sooner or later reach the blood stream, are sterile. I was surprised to learn that the Food and Drug Administration was not concerned in determining the sterility of products. My attention at the time was directed to this matter because a prominent internist had

asked me to examine three similar ampules which he had. I found in each a hemolytic *Staph. aureus*, which produced suppuration in rabbits. He had suspected that something was wrong, since injections of the other 9 ampules had produced abscesses in 4 patients. The other patients never came back, and he was wondering what was the matter. I immediately wrote an editorial in one of the journals, and it was at that time that the Food and Drug Administration proceeded to spend over \$25,000 in looking into the sterility of solutions for parenteral use throughout the country.

I, too, then began to examine the ampules on the market. Few stated that they were sterile. There was a statement as to contents, such as a solution of iron citrate or a solution of morphine sulfate.

More recently, as a member of the Sterile Advisory Board of the United States Pharmacopeia, I became concerned with the sterility of many of these products. Now we define a solution for parenteral injection, and therefore ampules and solutions for such use must be sterile, whether labeled so or not. The Food and Drug Administration and the manufacturers accept this policy. As a result, this class of marketable products is sterile, and we have had practically no trouble from that angle.

On the other hand, ointments are not sterile unless they are so labeled. I dare say that there are few sterile ointments on the market, whether used for ophthalmologic or other surgical work. I have examined ointments in tubes and in jars and have found them revealing the presence of bacteria.

The whole question of sterility is intricate and frequently complex. One must bear in mind, of course, that there is the matter of price; the economic question affects the picture. I, for one, have always stated that the question of price should not enter into the consideration if one wants a finished preparation which one feels assured is sterile. I recall when surgical gut became official in the "Pharmacopeia." At that time I, and members of our committee, went on record as stating that individual strands should be kept in individual hermetically sealed glass tubes. This form of marketing was first official in the twelfth edition of the "Pharmacopeia," and it is official in the thirteenth edition. At one time many strands were kept in one container. This was objectionable, for the same reasons that Dr. Lehrfeld has presented.

Now, with respect to ointments, one must bear many facts in mind. Dr. Lehrfeld mentioned various ointments which for the moment one might think were bactericidal. However, this is not always the case. The sulfonamide compounds, for instance, are only bacteriostatic; they are not bactericidal. They do not kill even if used internally, let alone when applied in ointments. One is prone to forget that when one speaks of a bactericidal effect one may think that all species of micro-organisms are killed. That is not so. The sulfonamide compounds are effective only against certain groups of organisms. The same holds true for penicillin. Even in the case of a bactericidal agent which is effective in suitable liquids, one will find that in ointments, unless the proper base, a water-miscible or a water-soluble base, is used, one may not get the same bactericidal or bacteriostatic effect; that is true, for instance, with phenol. A phenol ointment in a petrolatum base will have little antibacterial effect, but with a water-miscible base an entirely different effect is obtained.



As to the containers for ointments, I, for one, heartily endorse Dr. Lehrfeld's recommendation that certainly after operation a tube or container should be used only once for an open wound. If an ointment is to be used in ophthalmic surgery, it should certainly be sterile. Of course, the proper method of sterilization must be practiced. This may be difficult. It is not a simple procedure to market sterile ointments in small tubes or other individual containers unless the expense is considered, for it is an intricate, tedious, long-drawn-out process. The ointment tube itself, even the tubes for ophthalmic use, are generally primarily tin. Some of them contain about 0.75 per cent copper, added for hardening purposes. In the larger tubes of  $\frac{1}{2}$ , 1 or 4 ounce (15, 30 and 120 Gm.) capacity and larger, usually not used for ophthalmic products, lead, lined with tin, 7 per cent, is employed, and for toothpaste tubes 3 per cent tin is used. Some tubes may even have a plastic lining, but not the tubes for ophthalmic use.

It must be remembered that all tubes must be sterilized. The ophthalmic tubes of pure tin with the small amount of copper can withstand heat up to 400 F. My colleagues and I use dry heat at 160 C. (320 F.) for sterilization. The closures are generally of "bakelite," which may hold up at this temperature. The individual sterile tubes, then, must be filled with the sterile ointment under aseptic conditions. In many instances it may not be practical to sterilize the tube and contents or the final containers.

One may, of course, have individual sterile gelatin containers. All this means additional cost for the manufacturer. I assure you the pharmaceutical firms are willing to cooperate, but they consider the cost made necessary by the expense in producing such a preparation.

The question has been raised whether a bacteriostatic or bactericidal agent may be added which, when incorporated into an ointment, will result in a preparation that is self sterilizing. Zinc peroxide has been mentioned. This substance may be satisfactory, but in some instances it possesses irritating effects, especially in the eye. Urea peroxide has been recommended for sulfonamide ointments, but on standing the sulfonamide compound frequently becomes oxidized. The self-sterilizing agent not only must kill bacteria which are present but must be nonirritating; so a series of tests to prove that particular point must be conducted. Furthermore, one cannot usually say that because the zinc peroxide or the urea peroxide is effective in combination with the sulfonamide compounds it will be effective with other medicaments. The question of such factors as effectiveness, stability and harmlessness must be considered.

I recommend and heartily endorse individual containers for dispensing ophthalmic ointments, certainly for preparations used for surgical purposes. However, unless requests for sterile ointments are made specifically, unless there is a demand for them and unless individual physicians are willing to meet the additional expense involved, manufacturers will not market sterile ointments for use in ophthalmologic surgery.

DR. GEORGE DUBLIN, Philadelphia: My comments have to do with the effects of ordinary ophthalmic ointments on the eye. For many years I have noted untoward actions to the use of ophthalmic ointments. These reactions were noted particularly in cases in which foreign bodies had

been curetted from the cornea, and, as usual, an ointment containing tetracaine hydrochloride U.S.P. or butacaine sulfate U.S.P. was ordered. The corneal abrasion healed without much trouble, but I noticed a considerable number of punctate areas over the cornea which stained with the dye; these areas persisted for several days after the healing of the original corneal ulcer or the corneal abrasion.

At first, I thought that these abraded areas were due to a form of allergy. Later, it occurred to me that they might be due to mechanical irritation. There is no ointment in which the drug is completely dissolved; some of it remains in crystal form. The small crystals within the ointment, by their mechanical action, cause corneal abrasions.

At first, I wondered why these patients complained of vague symptoms such as scratchiness, a sensation of a foreign body and tearing in the presence of a quiet eye, until I routinely stained each patient's cornea with fluorescein sodium; to my surprise, I found a great number of staining areas. To eliminate the possibility that these reactions were allergic, I used these ointments in the fellow eye and noted the same reaction. I tried other types of ointments, and I found that, regardless of the type I used, even boric acid ointment, I got the same reaction in a great majority of cases. I felt that an abraded cornea, the result of the use of an ophthalmic ointment, is an excellent medium in which infection may develop. I reasoned that, instead of preventing an infection, I might be responsible for the development of a corneal ulcer. I have noted these reactions for several years; consequently, I have not used ophthalmic ointment when I could avoid it, since, in my opinion, liquid medication is as efficacious as, and probably considerably better than, the use of ointment.

# CLINICAL EXPERIMENTS WITH NEW WAYS OF INFLUENCING INTRAOCULAR TENSION

## I. Effect of Rice Diet

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AND

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**O**PTHALMOLOGISTS are far from understanding completely the mechanism of maintenance and regulation of the intraocular pressure. The supreme governing mechanism most probably consists in a combined action of hormonal and neural elements, similar to the pattern which exists with regard to the endocrine system.

Contradictory reports have been made concerning the influence on the intraocular pressure of the hormone of the posterior lobe of the pituitary gland. Franceschetti and Schläppi,<sup>1</sup> however, demonstrated that the increase or decrease of tension depends on the quantity of hormone in action. This shows how complicated the mechanism must be. Possibly other known or hitherto unknown substances may be involved.

The influence of the sympathetic and parasympathetic portions of the autonomic nervous system on various functions of the eyes has long been recognized. Hess<sup>2</sup> contributed further to knowledge of this action. From the charts recording his extremely interesting, and not yet published, results in producing a number of combinations of symptoms in various parts of the body by stimulation of minute circumscribed parts of the hypothalamus, it is evident that there is a definite area in the hypothalamus stimulation of which regularly produces a simultaneous rise in blood pressure and dilation of the pupil. Although Hess has not yet extended his experiments to the investigation of the intraocular pressure,

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1. Franceschetti, A., and Schläppi, V.: *Die Wirkung der Hormone des Hypophysenhinterlappens auf die Pupille und den intraocularen Druck*, Deutsche med. Wchnschr. 66:529, 1940.

2. (a) Hess, W. R.: *Vegetatives Nervensystem und Auge*, Klin. Monatsbl. f. Augenh. 77:289, 1926. (b) Hess, W. R., and Lehmann, F. E.: *Der Einfluss vegetativer Reizstoffe auf der Adeptier unzustand der Retina*, Arch. f. d. ges. Physiol. 211:603, 1926.

it might be well to search for a regulatory center of this kind in that area.<sup>3</sup>

Thus, whereas there is a general idea how a central governing mechanism for the regulation of the intraocular tension might be organized, the existence of such a center is hypothetical. A rational way of influencing the intraocular tension through that center, therefore, is still a remote possibility.

Much more definite is knowledge concerning local factors which influence the intraocular tension. It is understood that these local factors are under the influence of the hypothetical center in the hypothalamus. This, however, does not exclude the possibility of acting on these factors independently or the usefulness of such an attempt so long as one is unable to control the whole problem from a central point.

In principle, the local mechanism in the eye which controls the intraocular tension centers around the balance of inflow and outflow of the intraocular fluid.

The inflow depends partly on the conditions existing on either side of the blood-aqueous barrier. Among these conditions, the osmotic pressure, which is dependent on the concentration of electrolytes and nonelectrolytes; the size of the molecules involved, and the electric charge of the ions present are of paramount importance. From the research of Friedenwald and co-workers,<sup>4</sup> Duke-Elder and associates<sup>5</sup> and the Boston group, with Cogan, Kinsey, Grant, Jackson and Terry,<sup>6</sup> it would now seem that the old controversy as to whether the aqueous is formed by transfusion or secretion no longer exists. Electrolytes are shown to enter the anterior chamber by secretion, whereas nonelectrolytes enter by ultrafiltration. Moreover, the state of permeability of the semipermeable

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3. Personal communication to the authors.

4. (a) Friedenwald, J., and Stiehler, R. D.: Circulation of the Aqueous: VII. A Mechanism of Secretion of the Intraocular Fluid, *Arch. Ophth.* **20**:761 (Nov.) 1938. (b) Friedenwald, J. S.; Buschke, W., and Michel, H. O.: Role of Ascorbic Acid (Vitamin C) in Secretion of Intraocular Fluid, *ibid.* **29**:535 (April) 1943. (c) Friedenwald, J. S.: Dynamic Factors in the Formation and Reabsorption of Aqueous Humor, *Brit. J. Ophth.* **28**:503, 1944.

5. (a) Duke-Elder, S.; Quilliam, J. C., and Davson, H.: Some Observations on the Present Position of Our Knowledge of the Intraocular Fluid. *Brit. J. Ophth.* **24**:421, 1940. Duke-Elder, S., and Davson, H.: The Significance of the Distribution Ratios of Nonelectrolytes Between Plasma and the Intraocular Fluid, *ibid.* **27**:432, 1943.

6. (a) Kinsey, V. E.; Grant, M., and Cogan, D. G.: Water Movement and the Eye, *Arch. Ophth.* **27**:242 (Feb.) 1942. (b) Kinsey, V. E., and Grant, W. M.: The Secretion-Diffusion Theory of Intraocular Fluid Dynamics, *Brit. J. Ophth.* **28**:355, 1944. (c) Kinsey, V. E.; Jackson, B., and Terry, T. L.: Development of Secretory Function of Ciliary Body in the Rabbit Eye, *Arch. Ophth.* **34**:415 (Nov.) 1945.

membrane itself, which constitutes the blood-aqueous barrier, influences the exchange through this barrier. The permeability has been demonstrated to be qualitative, inasmuch as it depends on the size of the molecules which are supposed to penetrate it. The factors of simple hydrodynamic pressure and of the state of permeability of the blood-aqueous barrier have not been made sufficiently clear; they must have some influence.

The outflow of fluid from the eye may also be affected by the factors just mentioned, since the exchange through the blood-aqueous barrier may occur in either direction. In addition, there is definite evidence of a flow of fluid entering through the blood-aqueous barrier and leaving through Schlemm's canal. This has become even clearer since Asher<sup>7</sup> demonstrated the merging of the clear aqueous with the epibulbar venous system through the aqueous veins.

For many years, endeavors to solve the problem of regulation of the intraocular tension in glaucoma have been too much dominated by surgical thinking. The more one learns from recent research how subtle and complicated is the problem of the formation and circulation of the aqueous, the more one becomes aware of how clumsy and crude is the procedure of punching holes in the eyeball or coagulating the ciliary body.

The following clinical experiments have emerged from an effort to reverse this attitude of the deification of surgery. They are intended to serve as a contribution to knowledge of how the formation and circulation of the aqueous and the intraocular tension may be influenced by other than surgical procedures and miotics.

Three methods of influencing the intraocular tension were investigated: 1. Action of a particular diet on the composition of the blood and tissue fluids. 2. Reduction of the permeability of the blood-aqueous barrier. Experimental studies on animals concerned with the blood-aqueous barrier were conducted simultaneously by one of us (F.W.S.) and were reported elsewhere.<sup>8</sup> 3. Direct action on the sympathetic and parasympathetic nervous system. This method will be the object of the third study. The present study is concerned with the first method, that of the influence of diet.

#### INFLUENCE OF RICE DIET ON INTRAOCULAR TENSION

Not much is known about the factor of diet except that the intraocular tension is always lower after meals (Pissarello<sup>9</sup>). Kempner<sup>10</sup> demon-

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7. Asher, K. W.: Aqueous Veins: Preliminary Note, *Am. J. Ophth.* **25**:31, 1942.

8. Stocker, F. W.: Experimental Studies on the Blood-Aqueous Barrier: II. and III., *Arch Ophth.* **37**:583 (May) 1947.

strated that a diet limited to rice, sugar, fruit and fruit juices, supplemented with vitamins and iron, had a beneficial influence on the course of hypertension on the basis of acute or chronic primary renal disease or of "hypertensive vascular disease." Exclusive of the patients who came in for treatment in such an advanced stage that they died within a short time, hypertension improved in 64 per cent of 167 patients, and the heart became smaller in 91.7 per cent. Of 33 patients with advanced hypertensive retinopathy, the condition became worse in 1, came to a standstill in 11 and improved greatly, or even cleared up completely, in 21. Kempner described his diet as follows:

The rice-fruit-sugar diet, which, for the sake of brevity, will be referred to as "the rice diet," contains in 2000 calories about 20 Gm. of protein, 5 Gm. of fat, 460 Gm. of carbohydrate, 0.2 Gm. of sodium and 0.15 Gm. of chloride. Patients with marked hypochloremia, or, with symptoms of salt deprivation, are given extra sodium chloride in small amounts, or hydrochloric acid. The fluid intake is usually limited to 700-1000 cc. of fruit juices per day (no water).

Dry rice contains about 350 calories per 100 Gm. The average patient can eat 300 Gm., or 10 ounces daily, which will provide about 1050 calories; the remaining 900 or 1000 calories must be supplied by the liberal use of sugar and fresh or preserved fruits. All fruits are allowed, with the exception of nuts, dates, avocados, and any dried or canned fruit, or fruit derivatives, to which substances other than sugar have been added. *No salt is permitted.* All fruit juices are allowed, but tomato or vegetable juices are not. Brown or white sugar may be used *ad libitum*. Any kind of rice is used. The rice is boiled or steamed in plain water or fruit juices, without salt, milk or fat.

The patient should receive daily as minimal doses: Vitamin A, 5000 units; vitamin D, 1000 units; thiamine chloride, 5 mg.; riboflavin, 5 mg.; niacinamide, 25 mg.; calcium pantothenate, 2 mg.; ferrous sulfate, 0.6 Gm.

The effect of such a diet on certain groups of hypertensive patients is unique and has not been attained by any heretofore known low protein, low salt or other diet. A specific factor seems to be connected with the rice, although its existence has not yet been proved to complete satisfaction. Assuming that the intraocular tension is dependent in part not only on the blood pressure but on various factors, including chemical constituents of the blood and tissues, we were interested in investigating the effect which a strict diet of this type might have on the intraocular pressure.

*Material.*—A group of 20 patients were examined. Three of them had to be excluded from the study because they left the hospital after the first examination and did not return for follow-up study. Three were not on a rice diet and served as controls. Two came in for observation of the intraocular tension only after they

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9. Pissarello, C.: Importanza del rilievo della curva giornaliera di pressione oculare per la diagnosi precoce e per la cura del glaucoma, *Ann. di ottal. e clin. ocul.* 44:230, 1915.

10. Kempner, W.: Compensation of Renal Metabolic Dysfunction, *North Carolina M. J.* 6:61 and 117, 1945.

had already been on a rice diet. These also served as controls. On 12 patients, we were able to measure the intraocular tension before institution of the rice diet and afterward at regular intervals for an average period of seven and a half weeks. One patient could be followed for only three days. No other period of observation was shorter than ten days. One patient was examined eighteen weeks after the first examination.

*Technic.*—As long as the patient stayed in the hospital, all measurements of intraocular tension were made in the morning before he had been up, and before he had eaten breakfast. With this routine, the influence of any particular time of the day, of the position of the body and of intake of food was eliminated. Some of the later examinations, after the patient had left the hospital, had to be made at any time of the day, whenever the patient happened to return. All measurements were taken by the same person and with the same Schiötz tonometer.

*Readings for Intraocular Tension and Blood Pressure for Subjects 1 and 2*

Subject	Diet Before (b) and After (a) Rice Diet Was Instituted	Intraocular Pressure, Mm. (Schlotz)		Blood Pressure, Mm. Hg.	
		Right Eye	Left Eye	Systolic	Diastolic
1	9/2/45 (b)	22	25	240	120
	9/5/45 (a)	19	18	200	113
2	1/14/46 (b)	22	22	188	110
	1/25/46 (a)	15	13	184	110

The results of simultaneous measurements of the intraocular and the systolic and diastolic blood pressures are recorded in the table and in charts 1 to 5.

In the 12 patients who remained after elimination of the 8 patients, a striking reduction in intraocular pressure was observed as soon as the rice diet was instituted. The degree of reduction varied from patient to patient and during the course of the treatment, but reductions of 5 to 7 mm., persisting over long periods, were not uncommon. In most patients a parallel decrease in the systolic and diastolic blood pressures was observed. It was possible, therefore, that the reduction in intraocular pressure was simply the result of the reduction in arterial pressure. However, there was no definite parallelism between the decrease in tension in the two systems. Some patients who responded with a sharp lowering of blood pressure had only moderately reduced intraocular pressure,<sup>11</sup> and patients with relatively poor response of the blood pressure showed a considerably lower intraocular pressure.<sup>12</sup> The two groups of controls also gave interesting information as to the relation of intraocular tension and blood pressure. Patients who were not given a rice diet did not show an equally great reduction of intraocular

11. Kinsey and others.<sup>6a</sup> Asher.<sup>7</sup>

12. Hess and Lehmann.<sup>2b</sup> Friedenwald and Stiehler.<sup>4a</sup> Friedenwald, Buschke and Michel.<sup>4b</sup>

tension, even if the blood pressure was reduced by other measures<sup>13</sup>; nor did the patients who had been given a rice diet before the intraocular tension was taken show any additional reduction when further measure-

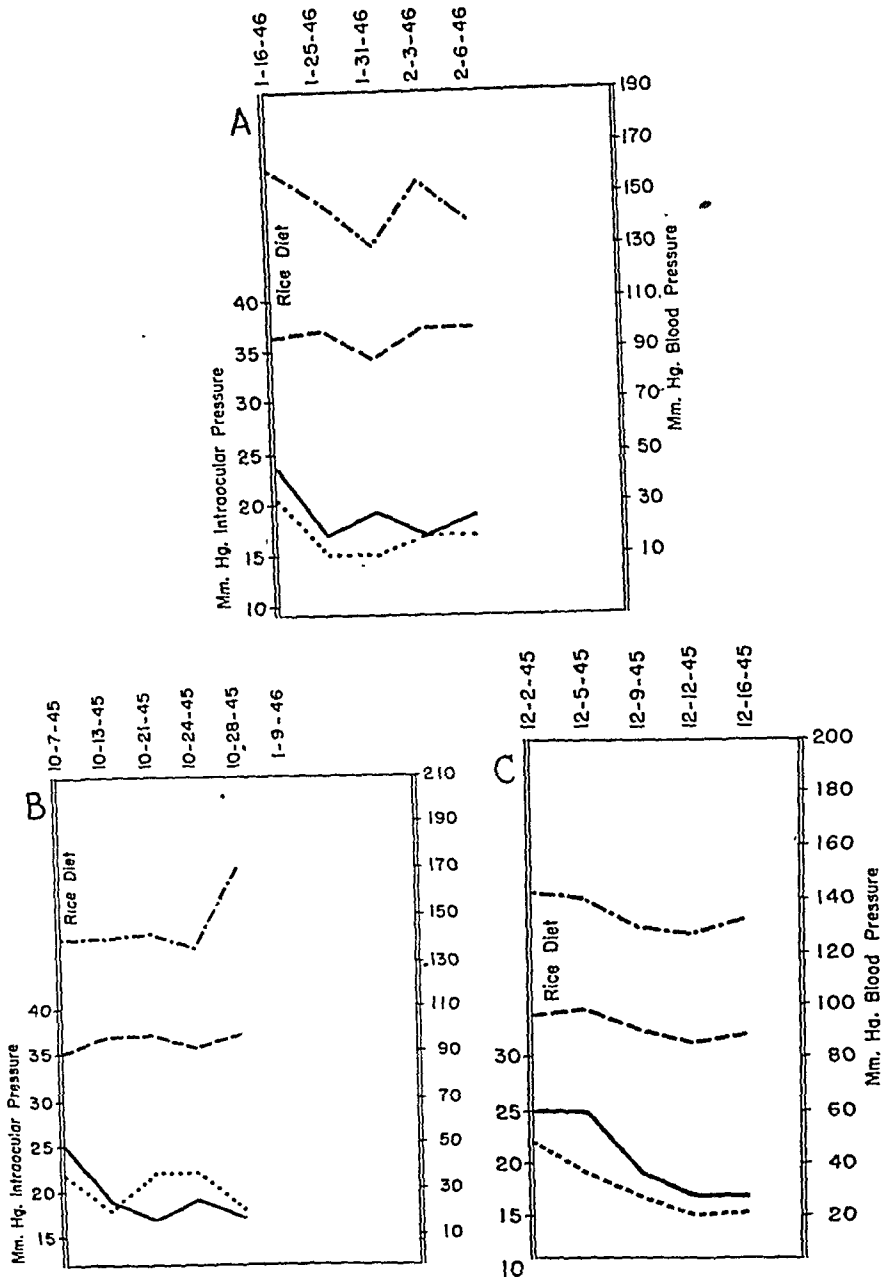


Chart 1 (subjects 3 to 5).—Relation of intraocular pressure to blood pressure.

In this chart, and charts 3 to 5, the line of dots and dashes indicates the systolic blood pressure; the line of dashes, the diastolic blood pressure; the solid line, the intraocular tension in the right eye, and the line of dots, the intraocular tension in the left eye.

ments were made. The striking irregularity in both intraocular tension and blood pressure in patient 8 might be explained on the basis that this patient was highly nervous and excitable.

13. Stocker.<sup>8</sup> Pissarello.<sup>9</sup>



These facts, indeed, point to the conclusion that it cannot be merely the decrease in blood pressure that influences the intraocular tension;

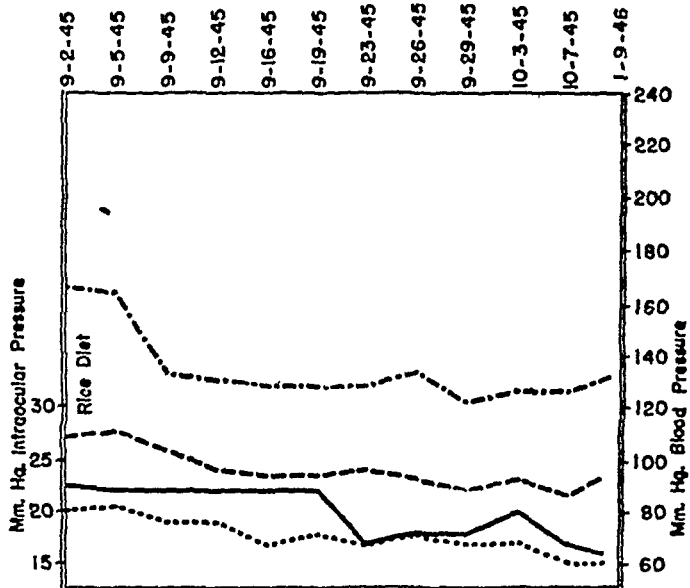


Chart 2 (subject 6).—Relation of intraocular tension to blood pressure.

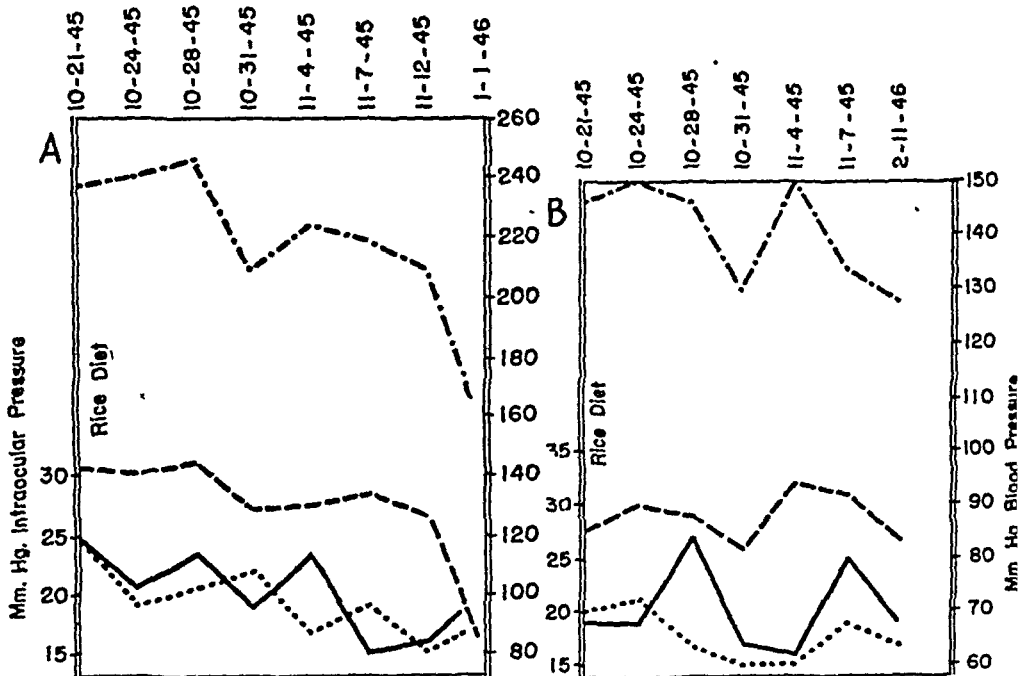


Chart 3 (subjects 7 and 8).—Relation of intraocular tension to blood pressure.

rather, there must be some specific effect of the rice diet. What may be the factor that produces this remarkable decrease in intraocular tension?

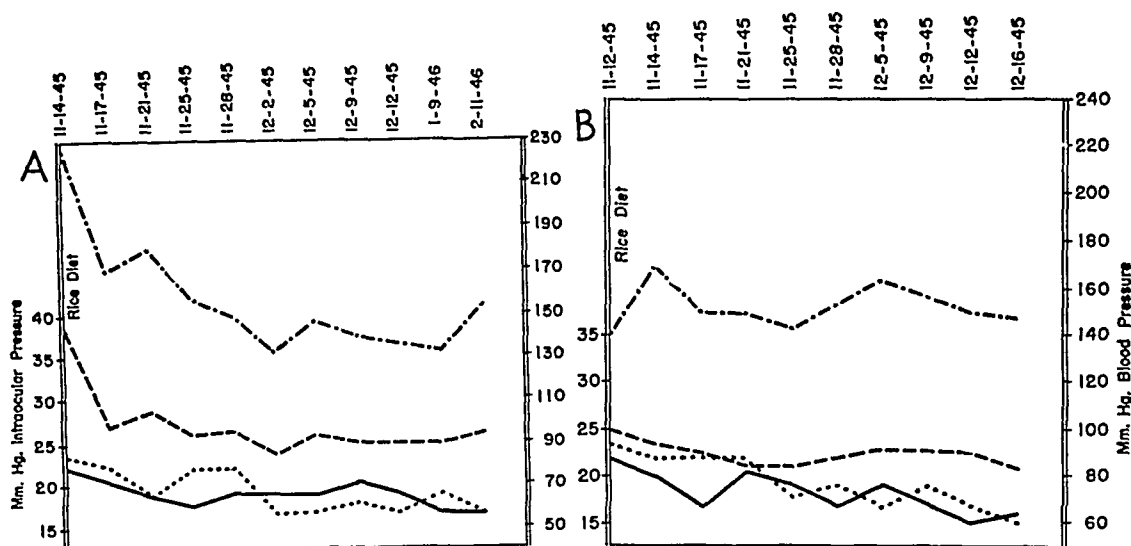


Chart 4 (subjects 9 and 10).—Relation of intraocular pressure to blood pressure.

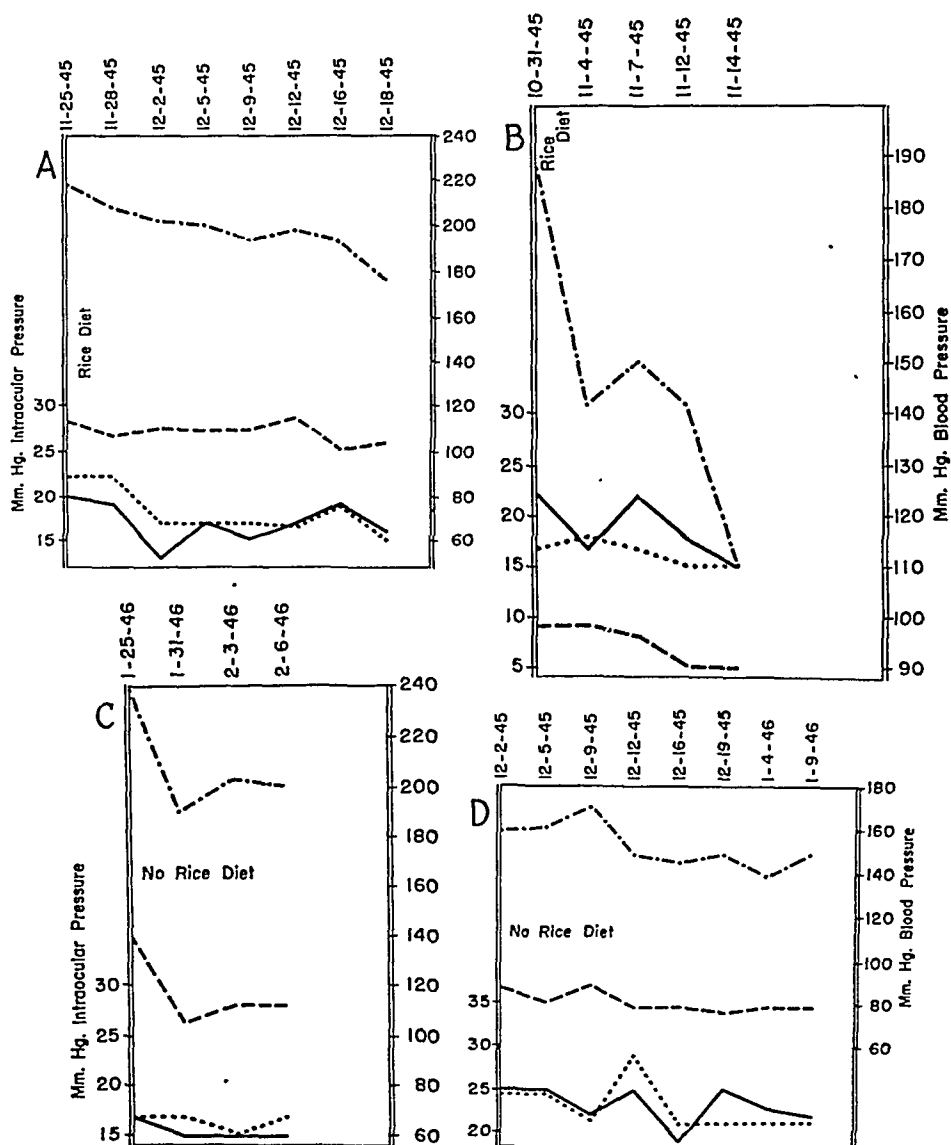


Chart 5 (subjects 11-14).—Relation of intraocular tension to blood pressure.

The influence of the rice diet on metabolism and the blood chemistry was extensively studied by Kempner. Here are some of the main facts: In spite of the low protein intake, the protein equilibrium of patients on the rice diet was maintained. Striking was the decrease in excretion of chlorides in the urine. In a typical case urine chlorides which had measured 83 and 73 milliequivalents while the patient was given a regular hospital diet decreased to 47 milliequivalents after only two days of rice diet and were found to be 2.7 and 3.2 milliequivalents after twenty-one and twenty-six days of rice diet, respectively. On the other hand, the reduction of plasma chlorides did not reach the critical level. Average values for 91 patients were 97.0 milliequivalents before and 91.7 milliequivalents after an average of forty-four days of rice diet.

The explanation of the phenomenon of the reduction in intraocular tension by the rice diet is still hypothetical. For a time we thought that a relative depletion in chlorides of the tissues brought about by the low chloride rice diet might have something to do with it. But recently we are more inclined to attribute the drop in tension to a possible reduction in the secretion of sodium by the ciliary body. This would be in line with the changes taking place in the kidney. There the process is one not of secretion, but of reabsorption of sodium in the tubules, which is diminished after the use of the rice diet. But, whatever the explanation may be, the fact exists that in certain circumstances the intraocular tension may be influenced by dietary measures.

The rice diet is essentially a low protein, low chloride and low sodium diet. Whether a specific factor, pertaining to the rice as such, contributes to the spectacular results in certain cases of arterial hypertension has not yet been ascertained. For the explanation of the reduction of the intraocular tension, the assumption of such a factor does not seem necessary.

The group of patients who showed such a remarkable decrease in intraocular tension after they had been given a strict rice diet had arterial hypertension. They showed various degrees of hypertensive alterations in the eyeground, but none of them had glaucoma. From the standpoint of intraocular tension, they were to be considered normal. How glaucomatous patients will react to the same diet will be demonstrated by another series of experiments and reported on completion of the study.

## SUMMARY

The influence of the "rice diet," as introduced by Kempner for the treatment of hypertensive vascular disease, on the intraocular tension of nonglaucomatous patients was studied. All patients subject to this diet showed a striking and persistent reduction of intraocular tension. The reduction of the intraocular tension did not seem to be directly dependent on the reduction of the blood pressure. It is believed that a relative depletion of chlorine and sodium ions in the body tissues, including the eye, might be the underlying factor in this phenomenon.

1110 West Main Street.

## TUMORS OF THE OPTIC NERVE

Long Survival in Three Cases of Intracranial Tumor

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THE OPTIC nerve, by virtue of its anatomic position, acts as a pathway for disease within the orbit, on the one hand, and disease within the cranium, on the other. Because of this fact, it is not surprising that the interdependence of ophthalmologists and neurosurgeons with regard to certain problems concerning tumors of the optic nerve continues to exist. A discussion of some aspects of these tumors will serve to illustrate this relationship.

The earlier communications concerning tumors of the optic nerve were confined almost solely to their intraorbital manifestations. The characteristic history of a child with progressive loss of vision in one or both eyes together with painless unilateral proptosis was in itself suggestive of an intraorbital tumor of the optic nerve. With the development of neurosurgery, the region of the optic chiasm became exposed with greater frequency and safety. Craniotomy performed in search of an intrasellar or a suprasellar lesion disclosed on rare occasions a tumor of the chiasm or of the optic nerve itself. The diagnosis of neoplasms in the latter site is based on evidence subtler than that presented by their orbital counterpart, but it is well to remember that tumors of the optic nerve, whether along its intracranial portion or within the orbit, are in fact the same disease.

Scarpa,<sup>1</sup> in 1816, made notes about a patient with an orbital tumor which seemed to take its origin from the sheath of the optic nerve. There is little question, however, that Wishart,<sup>2</sup> in 1833, was the first

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1. Scarpa, cited by Byers;<sup>3</sup> cited by Demarquay: *Traité des tumeurs de l'orbite*, Paris, V. Masson, 1860.

2. Wishart: A Case of Extirpation of the Eyeball, *Edinburgh M. & S. J.* 40:274, 1833.

to describe the lesion clearly. Some excerpts from his case report are of unusual interest and are presented here:

Euretta Douglas, age 13. On her looking downwards with the eye a firm tumor can be distinctly felt near the situation of the lacrymal gland. . . . For the first three months nothing was done for it; but after that there was such a rapid increase in size that the surgeon who was consulted pronounced it to be dropsy of the eye. He applied leeches over the eyebrow and blisters to the temple without producing any mitigation of the symptoms. . . . At a consultation with Dr. Gillespie and Prof. Lizars it was agreed that nothing could be done to save the eye. . . . I removed the eye, assisted by the gentlemen and Mr. Burt on the first of March.

On examination of the eye after its removal the disease was found to be seated in the substance of the optic nerve; the coat of the nerve being very much distended and evidently forming the outer cover of the tumor. . . . The tumor was of a firm consistency resembling cerebral substance, generally considered of a malignant nature. I have never met with any cases of the same description (as this) in the works of surgery or morbid anatomy which I have examined. The only one resembling it is related by Panizza in his work "*Sul Fungo Midollare*" in a little girl six years of age in which there was found on dissection not only a small tumor surrounding each optic nerve but a still larger cerebral mass at the base of the brain.

The tumor described here by Wishart was undoubtedly a glioma of the optic nerve. As will be pointed out later, this type of tumor should be classified as an intraneural tumor of this structure.

In Wishart's reference to the patient of Panizza, it is fairly clear that the tumor described originated intracranially and extended into the orbit. Extension from the orbit to the intracranial cavity is, however, perhaps more frequent. In 191 cases of tumor of the optic nerve studied independently by Byers<sup>3</sup> and Hudson,<sup>4</sup> evidence of definite intracranial involvement was presented in 40 (21 per cent). This percentage must, of course, be considerably higher, since the terminal events in the lives of most of the patients are not known. In only 8 of Byers' 112 cases was the patient known to have remained well for more than five years. In a collective survey of the cases reported by Byers and by Hudson, 23 postmortem examinations were noted. Of these, 21 revealed intracranial extension. Fourteen of the 21 necropsies were performed on patients who died of postoperative meningitis, and it should be noted that these 14 patients had intracranial spread of the tumor at the time of the treatment of the orbital tumor.

From all this, it can be appreciated that a tumor of the optic nerve, whether intraorbital or intracranial, represents a single lesion possessing at least the potentiality of spreading from the orbit to the chiasmal

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3. Byers, W. G. M.: Primary Intradural Tumors of the Optic Nerve: Fibromatosis Nervi Optici, *Stud. Roy. Victoria Hosp., Montreal* 1:3-82, 1901.

4. Hudson, A. C.: Primary Tumors of the Optic Nerve, *Proc. Roy. London Ophth. Hosp. Rep.* 18:317-439, 1912.

region or in the opposite direction. On the other hand, Byers,<sup>3</sup> in 1901, wrote:

. . . when a primary tumor of the optic nerve causes death it is, I believe, never because of a spreading backward of the orbital tumor but through the continued growth of an intracranial portion of the neoplasm which coexists with the orbital tumor and which is not removed at the time of operation. . . . It may be that the removal of the orbital portion [of the tumor] may in some way retard or stop the growth within the skull . . . but it is highly probable that in the majority of these cases the unexcised cerebral (tumor) continues on its course of development and sooner or later brings about the death of the patient.

The description of the types of tumors of the optic nerve remained in a chaotic state until Hudson,<sup>4</sup> in 1911, brought order to the subject in his classic paper. He designated three types of tumors, namely, the neoplasms characterized by gliomatosis (gliomas), the endotheliomas and the tumors characterized by fibromatosis of the nerve sheath (fibromas). In a comprehensive review of the clinical and pathologic aspects of tumors of the optic nerve, Davis<sup>5</sup> stated that most authors are now agreed to the general classification given by Hudson. Davis reviewed 305 cases reported up to 1934 and tabulated them as follows:

Gliomatosis (glioma) .....	193	(probable and certain)
Endotheliomas .....	86	(probable and certain)
Fibromatosis of the sheath .....	8	
Diagnosis uncertain .....	18	
	305	

The classification of tumors of the optic nerve was further simplified by Verhoeff,<sup>6</sup> who divided them into two general groups: (1) intraneural tumors of the optic nerve, namely, the gliomas arising within the nerve stem; and (2) extraneural tumors of the optic nerve, arising in the nerve sheath and comparable to the meningiomas of the brain. Verhoeff's classification, aside from its simplicity, has still another virtue. It recognizes the embryologic and histologic characteristics which make the second nerve unique. Wolff<sup>7</sup> expressed the situation well in these words: The optic nerve is no nerve at all but part of the brain and its tumors will be in all essential features identical with those of the brain; and just as there is only one brain tumor, the glioma, so there is only one intraneural tumor of the optic nerve, also the glioma.

The extraneural tumors of the brain and optic nerve arise from the meninges. These tumors (meningiomas or endotheliomas) characteristi-

5. Davis, F. A.: Primary Tumors of the Optic Nerve (Phenomenon of von Recklinghausen's Disease): A Clinical and Pathologic Study with a Report of Five Cases and a Review of the Literature, *Arch. Ophth.* **23**:735-821 (April); 957-1022 (May) 1940.

6. Verhoeff, F. H.: Primary Intraneural Tumors (Gliomas) of the Optic Nerve, *Arch. Ophth.* **51**:120-140 (March); 239-254 (April) 1922.

7. Wolff, E.: Discussion on Tumors of the Optic Nerve, *Proc. Roy. Soc. Med.* **33**:685-692, 1940.

cally compress and indent the underlying nerve elements but do not invade nerve structures.

Until 1911, when Hudson published his review of the tumors of the optic nerve, there were less than 350 reported cases. The ratio of intraneural to extraneural growths was 3:1. Both types were commoner in the female. The age of onset of symptoms in patients with tumors of these two types is especially noteworthy. Of the 118 cases of intraneural tumors summarized by Hudson, symptoms were presented in the first ten years of life in 75 per cent and in the first five years in 40 per cent. There were 29 cases of extraneural tumors in Hudson's review. Of these, the onset of symptoms was in the first decade of life in only 10 per cent, while in 50 per cent symptoms first developed after the thirtieth year.

According to Verhoeff, the high percentage of cases of intraneural tumors in which symptoms develop early in life "suggests they are congenital in origin and due to some more or less localized abnormality of embryonic development of neuroglia of the nerves." More than 50 per cent of the patients with extraneural tumors of the optic nerve begin to show symptoms after the thirtieth year. This type of tumor of the optic nerve is said to cause intracranial involvement about as frequently as does the intraneural type.

Although intraneural tumors (gliomas) tend to grow backward toward the brain, an extension forward sometimes occurs. Case 1 in the series reported by Verhoeff was the only one described up to that time in which the tumor spread distally to involve the globe. Other cases of spread of tumor tissue into the nerve head have since been reported; our case 3 is a probable instance of distal spread.

The intraneural tumor or glioma of the optic nerve spreads by direct extension. The mechanism of this spread has been studied in great detail. The theory expressed by Councilman<sup>8</sup> is perhaps the most plausible. He stated:

Advance of the tumor is preceded by general proliferation of the neuroglia cells which become converted into cells of the tumor and have the growth and form characteristic of these. It is impossible to avoid the impression that in the tumor or in some way associated with it a substance is produced which stimulates the neuroglia to growth. This growth takes the form of both general gliosis and of tumor. . . . The only changes which take place in the ganglion cells are those of atrophy and degeneration. They never take part in the formation of the tumor.

The good results which have been achieved by incomplete removal of the intraorbital gliomas of the optic nerve lend credence to this theory. Verhoeff noted that "removal of the largest part of the tumor may do away with the assumed stimulating substance and thus prevent

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8. Councilman, W. T.: Anatomical Considerations of Tumors of the Brain with Special Reference to the Gliomata, *Colorado Med.* 12:289, 1915.



further extension of the growth." In Hudson's review of 118 cases of intraneural tumors it can be seen that after incomplete removal of the intraorbital lesion local recurrence was rare.

The diagnosis of tumors of the optic nerve is not difficult when the neoplasm is confined to the orbit. Both the intraneural and the extraneural orbital growths cause unilateral exophthalmos, followed by progressive amaurosis. The impairment in vision sometimes precedes the proptosis in cases of intraneural tumor. The exophthalmos is usually

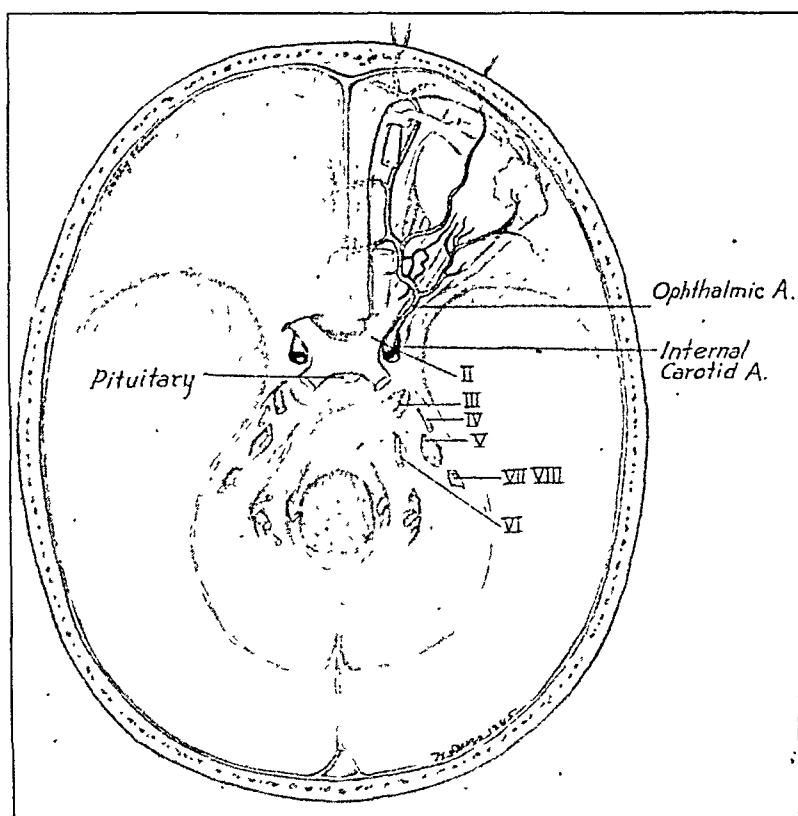


Fig. 1.—Sketch showing the general relationship of the optic nerves and chiasm of the sella turcica, the internal carotid arteries and neighboring cranial nerves (adapted from Spalteholz "Handatlas der Anatomie des Menschen" and "Gray's Anatomy").

painless. Pain in and limitation of movement of the eyeball are more commonly observed in patients with extraneural tumors.

In the event that a tumor of the optic nerve is confined to or spreads along the intracranial portion of the nerve, the diagnosis becomes somewhat more difficult. The clinical symptoms often simulate those of other tumors in the suprasellar or chiasmal region. The common features include primary atrophy of the optic nerve, changes in the visual fields and a deformed or enlarged sella. In addition, there may be suprasellar shadows, oculomotor palsy, diabetes insipidus, som-

nolence, obesity and secondary disturbances of the pituitary gland. The likelihood of such symptoms is evident if one bears in mind the relation of the optic nerves and chiasm to the neighboring structures (fig. 1). Dandy<sup>9</sup> expressed the belief that one should always think of a tumor of the optic nerve in any case of unexplained blindness. Roentgenographic evidence of an enlarged optic foramen or erosion under the anterior clinoid process is significant. This point was brought out by Martin and Cushing<sup>10</sup> and was also emphasized by van der Hoeve.<sup>11</sup> In cases in which symptoms point to the suprasellar region and no suprasellar shadow can be demonstrated in the roentgenogram the possibility of a tumor of the optic nerve should be borne in mind.

The detection of an enlarged sella turcica, bitemporal hemianopsia and primary optic nerve atrophy with evidence of pituitary deficiency would usually indicate an adenoma of the pituitary gland. However, these manifestations can be simulated to some degree by a tumor of the optic nerve, although as a rule the differentiation is not difficult. Actually, tumors of the optic nerve have for the most part been disclosed when the chiasmal region was explored with the expectation of finding a suprasellar lesion, such as a craniopharyngioma or a meningioma of the tuberculum sellae.<sup>12</sup>

Of the 345 verified intracranial gliomas of all kinds reported by Martin and Cushing<sup>10</sup> in 1923, 7, or 2 per cent, were chiasmal, and this number represented 0.84 per cent of all the 826 verified intracranial tumors in Cushing's series at that time. The relative frequency of these growths as they occur in the region of the sella was noted by Heuer.<sup>13</sup> In his review of 37 cases of chiasmal lesions, 73 per cent of the tumors were hypophysial, 24.3 per cent suprasellar and 2.7 per cent chiasmal.

It is obvious that the intrasellar tumors, by virtue of their somewhat more clearly defined clinical manifestations and their numerical preponderance, are more susceptible to accurate diagnosis than are the suprasellar growths, including tumors of the optic nerve, and that the differential diagnosis of a tumor in this region, either suprasellar or

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9. Dandy, W. E.: Prechiasmal Intracranial Tumors of the Optic Nerves, *Am. J. Ophth.* 5:169-188, 1922.

10. Martin, P., and Cushing, H.: Primary Gliomas of the Optic Chiasm and Optic Nerves in Their Intracranial Portion, *Arch. Ophth.* 52:209-241 (May) 1923.

11. van der Hoeve, J.: Roentgenphotographie des Foramen opticum bei Geschwülsten und Erkrankungen des Sehnerven, *Arch. f. Ophth.* 115:335-369, 1925.

12. Other lesions in the sellar region which on rare occasions may produce a similar clinical picture are gliomas of the infundibulum; parasellar, infrasellar and suprasellar aneurysms; an anomalous ophthalmic artery, and chiasmal arachnoiditis (either syphilitic or post-traumatic).

13. Heuer, G. J.: Surgical Experiences with an Intracranial Approach to Chiasmal Lesions, *Arch. Surg.* 1:368-381 (Sept.) 1920.

intracellular, is as a rule not difficult. On the other hand, the differentiation of certain craniopharyngiomas from tumors of the optic chiasm at times cannot be made with certainty. The accompanying table, adapted from Martin and Cushing,<sup>10</sup> is helpful in distinguishing between tumors of these types.

Ophthalmologists have been acquainted with tumors of the optic nerve for a longer period than have neurosurgeons. From the former's experience with the intraorbital portion of these growths, there developed the impression that tumors of the optic nerve were slow growing and that further growth of the neoplasm could be prevented or further diminished by incomplete removal of the lesion. For a time the prognosis of these tumors seemed hopeful. Byers, however, was among the first to realize that the disease was a serious one and that the real danger

*Differentiation of Suprasellar and Intracellular Tumors\**

Tumor or Craniopharyngeal Pouch	Tumor of Chiasm
Primary optic nerve atrophy, with edema superimposed in late stages, owing to hydrocephalus	Primary optic nerve atrophy; superimposed papilledema if intracranial pressure is increased; rarely, involvement of nerve head by tumor; exophthalmos with intra-orbital spread of tumor
Bitemporal hemianopsia; if vision lost in one eye, fairly acute vision retained in seeing half of other	Acuity low in both eyes, with fields showing less typical hemianoptic defects
Progress slow, often stationary for years	Progress on the whole more rapid and progressive
Sella variously deformed, enlarged or normal; posterior clinoid process more affected than anterior; suprasellar shadows common	In advanced stages, apparent extension of sella under anterior clinoid processes due to distention of optic foramina; no suprasellar shadows
Secondary manifestations of pituitary dysfunction common, with adiposogenital dystrophy and infantilism	Secondary manifestations of pituitary dysfunction inconspicuous; cutaneous indications of Recklinghausen's disease to be looked for

\*Adapted from the table of Martin and Cushing.<sup>10</sup>

was concerned with the spread of the tumor along the intracranial portion of the optic nerve. An intraorbital tumor of the optic nerve, in spite of the dramatic exophthalmos and amaurosis which it produces, does not endanger the life of the patient as does the less obvious intracranial tumor of this structure.

Evidence of the extremely poor prognosis of tumors of the intracranial portion of the optic nerve was presented by Martin and Cushing in their summary of the 7 cases of verified gliomas of the chiasmal region to which reference has been made. Three of their patients died after operation, of hyperthermia; 1 patient died six months after removal of a portion of the tumor along with the right optic nerve, and 2 patients died one year after operation. The seventh patient survived the exploratory operation for an unreported period. Such uniformly

unfavorable results following the operative treatment of these tumors led Martin and Cushing to write:

Unquestionably, if we may come in time to perfect our clinical diagnosis of these lesions, there is every reason to avoid operating upon them, though in cases of doubt an exploration may have to be made.

From our experience with the cases about to be reported, it would seem that such a pessimistic attitude is unwarranted. A more hopeful

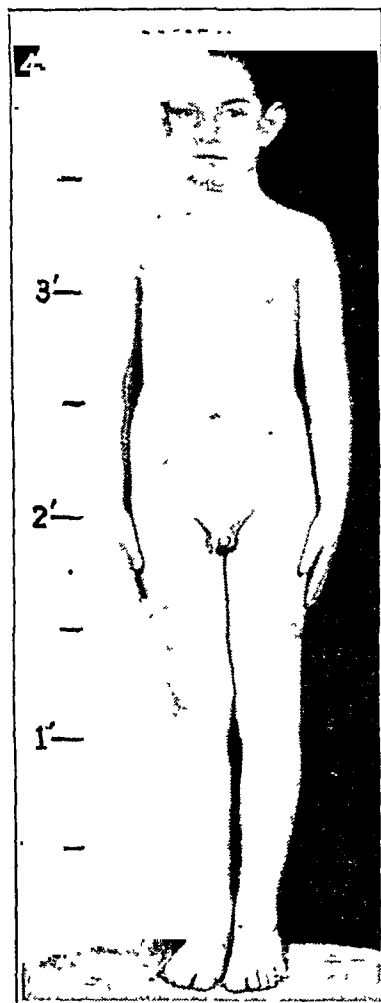


Fig. 2 (case 1).—Appearance before operation, showing slight secondary manifestations of hypopituitarism, a tendency to obesity and infantile genitalia.

note, likewise, has been sounded recently by Jackson,<sup>14</sup> who reported the removal of an intracranial glioma in a child  $4\frac{1}{2}$  years old. The patient was in perfect health eight and one-half years after the operation. Likewise, in this communication, Jackson gave an excellent summary of the symptoms, diagnosis and treatment of orbital tumors.

#### REPORT OF PERSONAL CASES

Since 1932, 3 patients with intracranial tumors of the optic nerve have been treated by one of us (G.H.) at the Lahey Clinic. For reasons

14. Jackson, H.; Orbital Tumours, Proc. Roy. Soc. Med. 38:587-594, 1945.

not apparent to us, all these patients have remained in remarkably good health over a period of years. It is now over twelve years since W.A. (case 1) was operated on and the diagnosis established histologically. This young man was in the Army of the United States in Germany and has recently returned home. M.H. (case 2) has been in good general health for over ten years after her craniotomy. The third patient (M.O'B.) was in excellent health at her last report, four and one-half years after operation.

The long periods of survival, in apparent good health, of these patients is noteworthy not only for its own sake but also in reevaluation of the prognosis of intracranial tumors of the optic nerve.

CASE 1.—W. A., an 8 year old boy, was seen at the Lahey Clinic on Jan. 22, 1934, having been referred by Dr. J. J. Skirball, of Boston. He was admitted to

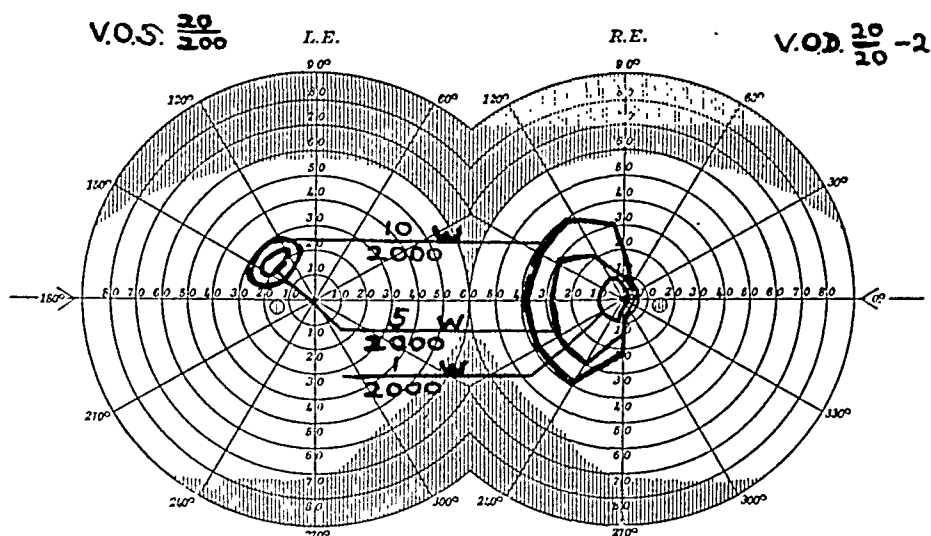


Fig. 3 (case 1).—Visual fields before operation (Jan. 22, 1934).

the New England Deaconess Hospital on the same date. The patient complained of failing vision in the left eye for the past year. During the preceding six months the left eye on occasion had turned in. One year earlier the school authorities notified the parents that the patient's vision was not up to standard, although it had previously been normal. Eye glasses were advised by the local physician. The left eye occasionally became inflamed and burned for the few months before his visit here. There was no diplopia. The patient was able to read well, but his mother thought that the vision was becoming progressively worse.

Examination revealed that the pupils were round, regular and equal and reacted to light and in accommodation. Extraocular movements were normal except for a few nystagmoid jerks to the right and left. The right fundus revealed moderate atrophy of the optic nerve; the optic cup was present, with slight engorgement of the veins. The left fundus presented a picture of advanced atrophy of the optic nerve; the optic cup was present, and the veins were greatly engorged. The sense of smell was intact bilaterally. The patient was inclined to obesity. He had hairless skin and infantile genitalia (fig. 2). Visual acuity was 20/20—2 in the right eye and 20/200 in the left eye. The visual fields before operation disclosed

temporal hemianopsia in the right eye and almost complete blindness in the left (fig. 3). Roentgenograms of the skull had been taken elsewhere, and the following report was sent to us: "There are definite erosion and depression of the anterior portion of the sphenoid bone at the edge of the sella in the region of the sulcus chiasmaticus. With this there are deep, hollowed-out areas under each anterior clinoid process, extending forward to the optic foramina. This is the appearance usually seen with gliomas of the optic chiasm (fig. 4) . . . The lesion in this case is inoperable as there is diffuse involvement of both nerves. The prognosis is eventually complete blindness. The only hope is that my diagnosis is incorrect."

In spite of this definite diagnosis from an expert roentgenologist, it was felt that the chiasmal region should be explored, in the hope that the lesion was of some other type.

*Operation.*—On Jan. 23, 1934, with the patient under anesthesia induced with solution of tribromoethanol U.S.P. and ether, right transfrontal craniotomy



Fig. 4 (case 1).—Roentgenogram of the sella turcica, showing hollowed-out areas under the anterior clinoid processes and displacement backward of the dorsum sellae.

was performed (G.H.). The dura was under increased tension and was opened. The right frontal lobe was retracted, revealing a suprasellar tumor, which was grayish red, soft and probably cystic. The impression at this stage in the operation was that the tumor was a cyst of Rathke's pouch. A needle was inserted, but no fluid could be aspirated. The right optic nerve was observed to be pushed laterally by the growth. The tumor capsule was cauterized and excised. Tumor tissue was removed with the pituitary spoon, and the tissue was noted grossly to resemble adenoma of the pituitary gland. A radical intracapsular evacuation of the growth was accomplished. The right optic nerve was thereby relieved of the pressure which was

stretching it, and this nerve settled back into its normal position with collapse of the capsule beneath it.<sup>15</sup>

*Pathologic Report.*—Sections stained with hematoxylin and eosin showed tissue composed almost entirely of astrocytes, which were greatly increased in number, atypical in pattern and with some variation in the configuration of nuclear form. In some foci these neoplastic astrocytes were condensed around an increased number of vascular channels, and they had a pronounced fibrillary pattern. This was brought out with a special stain, the glial fibrils forming a fairly dense meshwork.

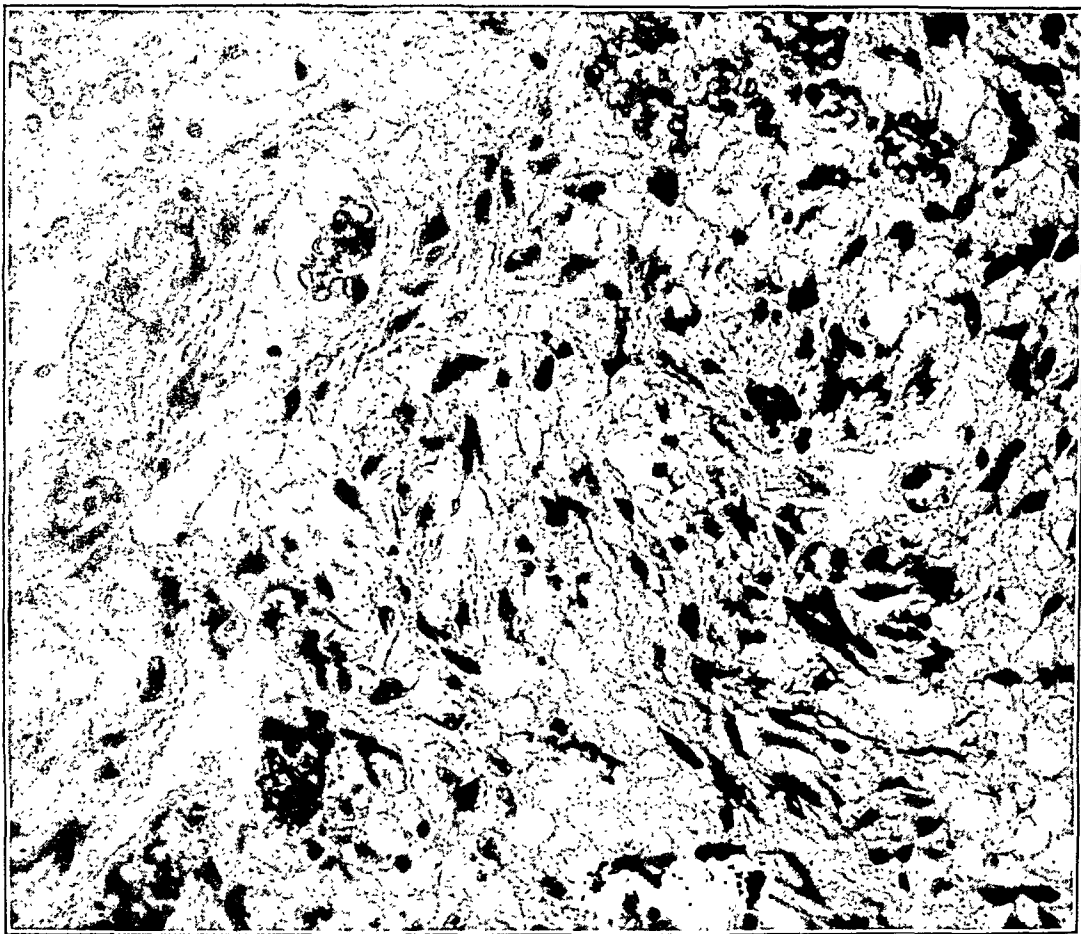


Fig. 5 (case 1).—Microscopic appearance of tumor, composed of fibrillary astrocytes.  $\times 350$ .

The diagnosis was fibrillary astrocytoma (fig. 5).

*Postoperative Course.*—The patient had an uneventful convalescence and noted some improvement of vision in the left eye. He was given four roentgen treatments in March 1934. He returned to school in September 1934 and achieved

15. It is interesting that in the operative note made by one of us (G.H.) it is stated that the left optic nerve was never visualized. It is probable that what was taken to be the tumor medial to the right nerve was actually the tumor incorporated in the substance of the left nerve and that the exit of the nerve from the skull could not be seen.

better grades than before operation. He returned yearly for examination, each time stating that the left eye had a tendency to turn inward after exercise and fatigue. His general health remained excellent, and he participated in active sports. At the age of 12½ years, pubic hair developed and the genitalia were normal, but there was no axillary hair. The right optic disk looked almost normal, but the left continued to show advanced primary atrophy of the optic nerve. The patient was seen in October 1940, at which time he was in good general condition, without complaints. Visual acuity and visual fields had remained almost exactly as they were before operation, and as taken four years after operation (fig. 6). A letter from the patient's mother, dated June 28, 1946, stated that the patient had been in the Army in Europe for a year and was in excellent health, awaiting transportation home. She enclosed a recent snapshot of the patient (fig. 7).

The patient himself returned to this country and reported for a personal check-up on Dec. 3, 1946. He was looking the picture of health (fig. 8). Subjectively and objectively, his vision had remained unchanged from that in the previous examinations.

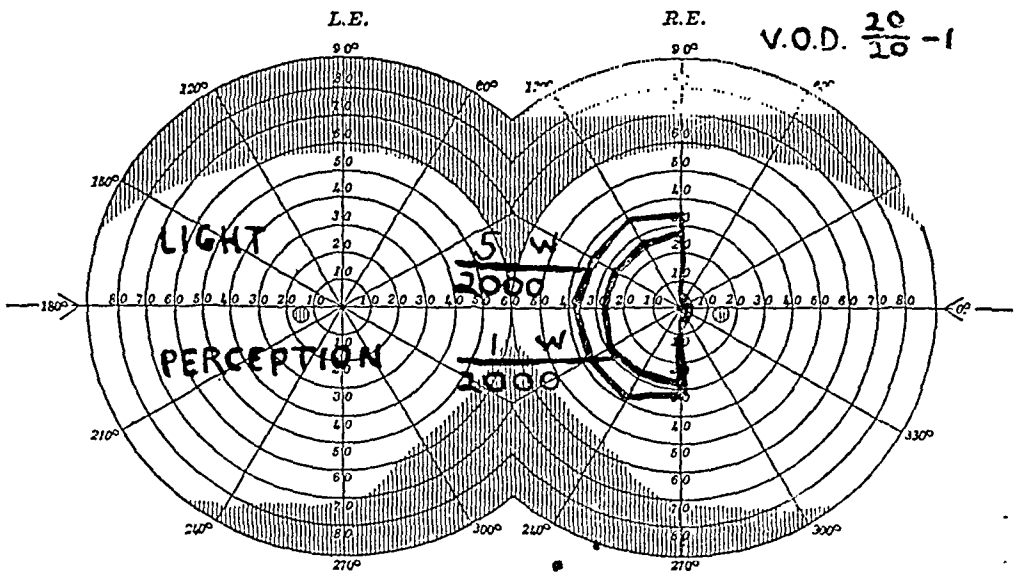


Fig. 6 (case 1).—Visual fields four years and ten months after operation (Nov. 25, 1938). These have remained unchanged up to the present time, twelve years after operation.

*Comment.*—The extraordinary story of this patient speaks for itself. His clinical picture and the gross appearance of the growth at the time of operation were so typical of a pituitary tumor (either adenoma or craniopharyngioma) that the eventual pathologic report came as a complete surprise. It is of considerable interest that the roentgenologist was able to make the correct diagnosis, but it is likewise fortunate that his advice as to the inoperability of the growth was not followed. How this patient could have been inducted into the Army, in view of his extremely limited vision, must remain a mystery.

It is now twelve years since the operation, and there is still no evidence that the tumor has extended or recurred. It is barely possible that the high voltage roentgen therapy which was given after opera-



tion may have had an inhibitory influence on the growth; although this is unlikely in cases of fibrillary astrocytoma, Dyke and Davidoff<sup>16</sup> expressed the belief that such treatment is helpful.

CASE 2.—M. H., a white married woman aged 52, was seen at the Lahey Clinic on Sept. 30, 1936, having been referred by Dr. William Allen, of Unadilla,

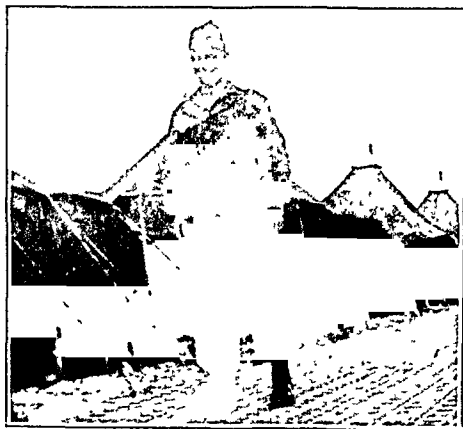


Fig. 7 (case 1).—Snapshot of patient while in the Army of the United States in Europe (1946), twelve years after operation.

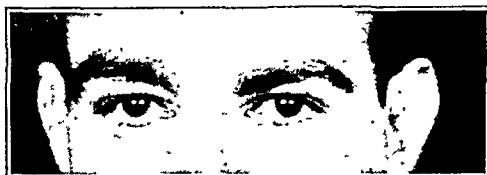


Fig. 8 (case 1).—Appearance of patient at last report, in December 1946.



Fig. 9 (case 2).—Appearance of patient before operation showing slight exophthalmos on the left.

N. Y., and on this date was admitted to the New England Deaconess Hospital. The patient's chief complaint was blindness in the left eye for one year. She recalled that she had always needed stronger glasses on the left side, but that four or five years prior to admission she had noted failing vision of the left eye.

16. Dyke, C. G., and Davidoff, L. M.: Roentgen Treatment of Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1942.

This had progressed until one year ago she was completely blind in the left eye. She recalled that the left temporal field disappeared first.

Physical examination revealed exophthalmos on the left side (fig. 9). With a base line of 109, readings of the exophthalmometer were 22 mm. for the left eye and 12 mm. for the right eye. The left pupil was larger than the right and reacted only in accommodation, but not to light. Extraocular movements were normal. The fundi revealed slight pallor of the right optic disk, with extreme pallor of the left. The veins were tortuous bilaterally. The remainder of the neurologic examination revealed nothing significant. Although the patient was completely blind in the left eye, the visual acuity and visual field of the right eye were normal (fig. 10).

Roentgenograms of the skull revealed a faint area of calcification above and anterior to the sella in the midline. In addition, the anterior clinoid processes were separated more than usual, and there was atrophy of the posterior clinoid process. These changes suggested a suprasellar tumor.

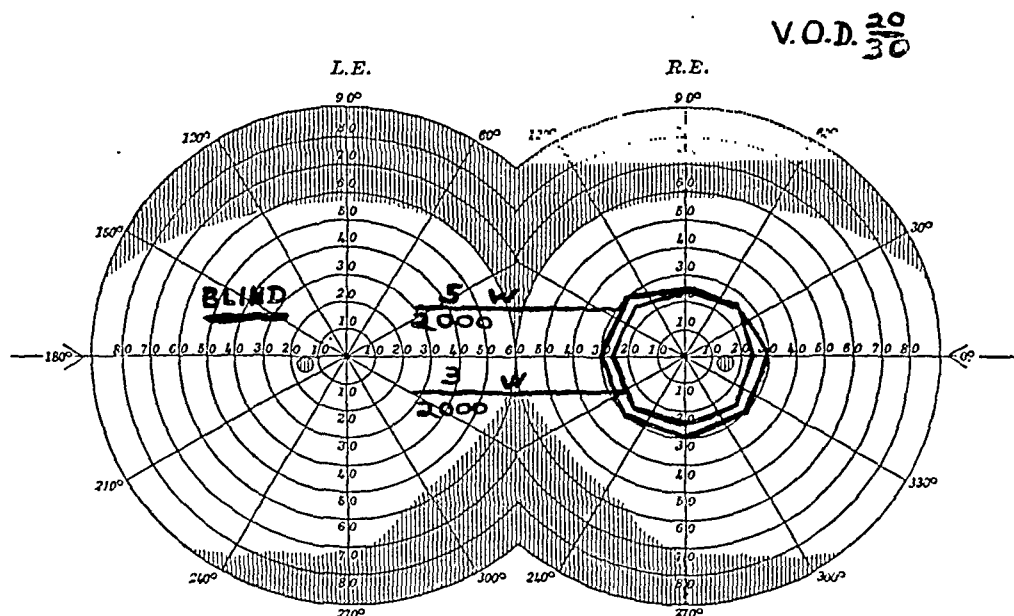


Fig. 10 (case 2).—Preoperative visual fields (Oct. 4, 1936).

*Operation* (Oct. 5, 1936).—A left frontal craniotomy was performed by one of us (G.H.). When the orbital plate was exposed, it was seen to be exceedingly thin, and it was therefore felt that an intraorbital tumor was present. The orbital plate was therefore removed and the capsule surrounding the orbital contents incised. This procedure permitted the structures within the orbit to bulge backward, with the release of high intraorbital pressure.

The frontal lobe was now retracted, and an unusual bulge in the region of the left optic nerve was disclosed. In order to secure satisfactory exposure, a portion of the tip of the left frontal lobe was excised. It was then possible to see that a tumor about the size of an English walnut was incorporated within the substance of the left optic nerve. It was grayish yellow, and its capsule was continuous with the sheath of the nerve.

The surface of the tumor was coagulated and then incised, after which the growth was removed piecemeal from within the capsule with the use of pituitary rongeurs, as well as by sharp dissection with knife and scissors, because of its fibrous nature. The growth apparently extended backward well into the left side of the optic chiasm, so that the removal was regarded as incomplete. The optic

foramen was completely decompressed, in addition to removing the orbital plate, as already noted.

*Postoperative Course.*—The patient made a good convalescence, and at the time of her discharge, on October 24, her physical status showed no essential change from that before operation. Her left eyeball had perhaps receded slightly (1 to 2 mm. on the exophthalmometer).

*Pathologic Report.*—Microscopic sections showed chiefly fibrosis. The tissue was composed chiefly of fibrocytes and narrow, interlacing bands of collagen.

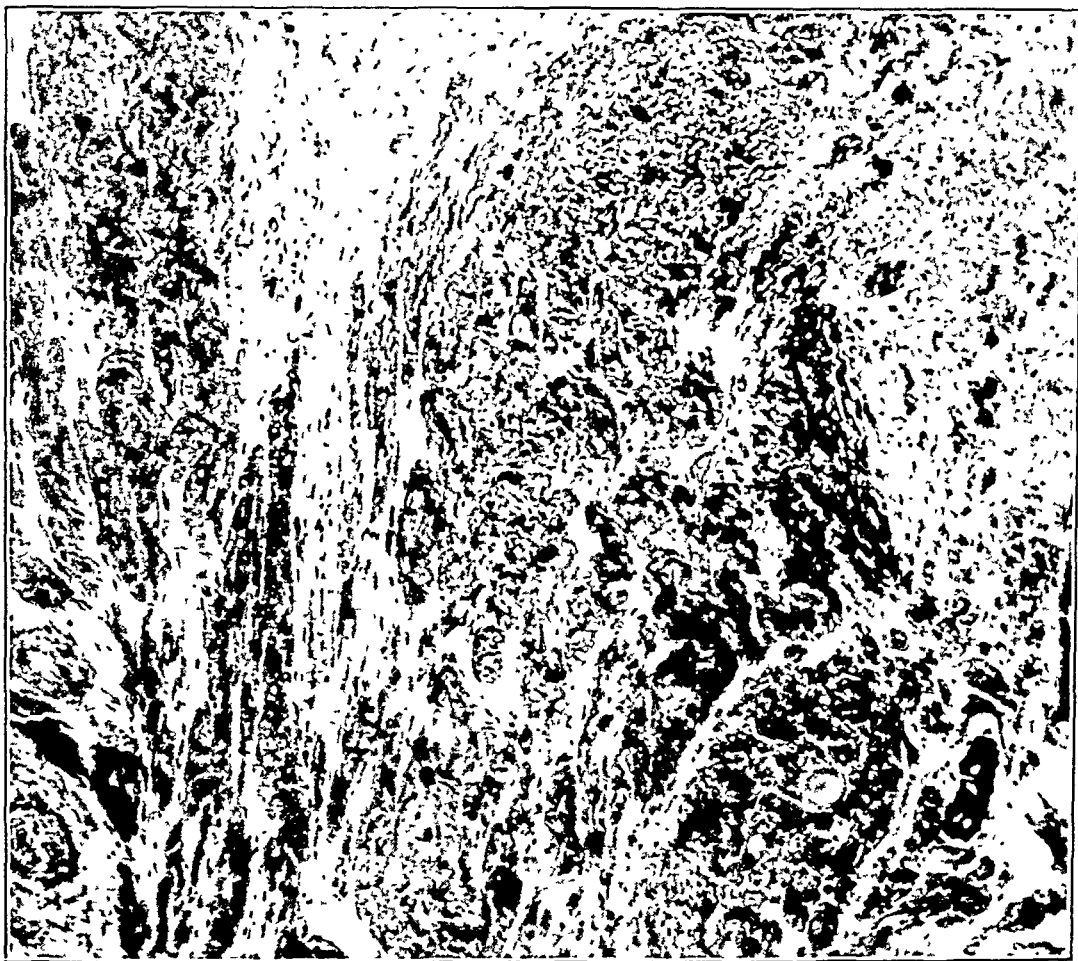


Fig. 11 (case 2).—Photomicrograph of tumor, showing its general fibrous character, together with areas of degeneration and obliterative endarteritis;  $\times 110$ .

While the fibrous tissue was not actively proliferating, much appeared to have been laid down recently. There were frequent irregular areas of partial tissue degeneration, some suggesting degenerated nerve tissue; in one of the areas there was a small focus of calcification. A scattering of hemosiderin was present throughout the tissue. Although there were few vessels of arteriolar size or larger, those that could be identified showed obliterative endarteritis, often to the point of complete occlusion. About some of these vessels was a cuff of lymphocytes with some polymorphonuclear neutrophils. An occasional venule also showed this perivascular cuffing. There were no mitotic figures, atypical cell or nuclear forms or other indications of neoplastic or rapid growth (fig. 11).

On June 28, 1944, the patient had a Miles resection for adenocarcinoma of the rectum and was in good health otherwise when she was discharged from the hospital after this operation, on Aug. 1, 1944, seven years and eight months after the tumor of the optic nerve had been removed. Her vision had remained the same as that before her intracranial operation. A letter from the patient, dated Jan. 13, 1947, ten years and four months after operation, stated that the sight of her right eye was as good as ever.

*Comment.*—From the clinical and neurologic standpoints, this woman had the symptoms of a retro-orbital tumor, such as a meningioma of the sphenoidal ridge, or possibly an aneurysm. The roentgenologic findings, however, did not support the evidence of a tumor of the sphenoidal ridge, but, rather, were in favor of a suprasellar growth because of the calcification above the sella. Again, the long period of survival (ten years and four months) is most encouraging, especially in view of the obviously incomplete removal of the tumor.

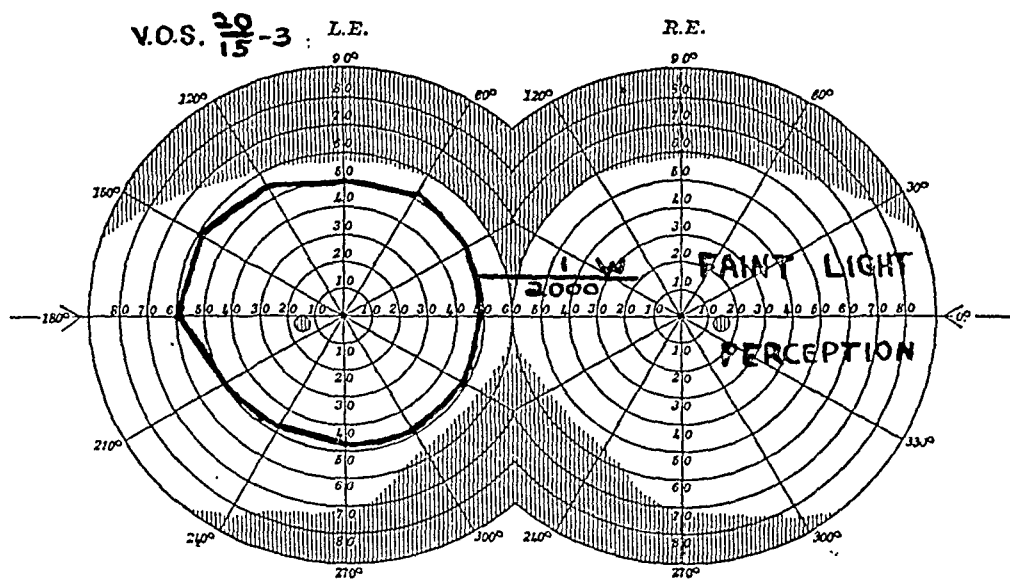


Fig. 12 (case 3).—Visual fields before operation (Oct. 22, 1941): normal vision in the left eye and the right eye practically blind.

Pathologically, this case must be regarded as one of the relatively rare instances of fibromatosis of the optic nerve, of which Hudson recorded 6 in his total series of 154 cases of tumor of the optic nerve.

CASE 3.—M. O'B., a single white girl aged 18, was seen at the Lahey Clinic on Oct. 10, 1941. She was referred by Dr. James C. McAdams, of Fall River, Mass. She complained of progressive loss of vision in the right eye during the fourteen months before examination. At the onset of her complaint the patient had first noticed blurring of vision in the right eye. The impairment in vision had been progressive, and when she was seen here practically no sight remained in the involved eye. She had never had any difficulty with the left eye. She recalled that in 1938 she had a series of severe headaches, lasting about a year. These attacks were chiefly fronto-occipital and required hospitalization. No diagnosis was made, however. In 1941 the patient had a period of unconsciousness, the duration of

which was not stated. Again, she was hospitalized for two weeks, but no diagnosis was made.

Examination revealed that the right pupil was slightly larger than the left and that the right pupil did not react well to light as compared with the left. The right fundus showed 4 D. of what was taken to be papilledema. The left fundus was normal. Extraocular movements were normal.

The exophthalmometric readings, with a base line of 95, were 19 mm. in the right eye and 17 mm. in the left eye. Visual acuity in the right eye was little more than faint light perception; that in the left was good, being 20/15—3. Since the patient was practically blind in the right eye, the visual field on this side was not obtainable. The visual field on the left side was normal, with a 1 mm. test object at 2 meters (fig. 12).

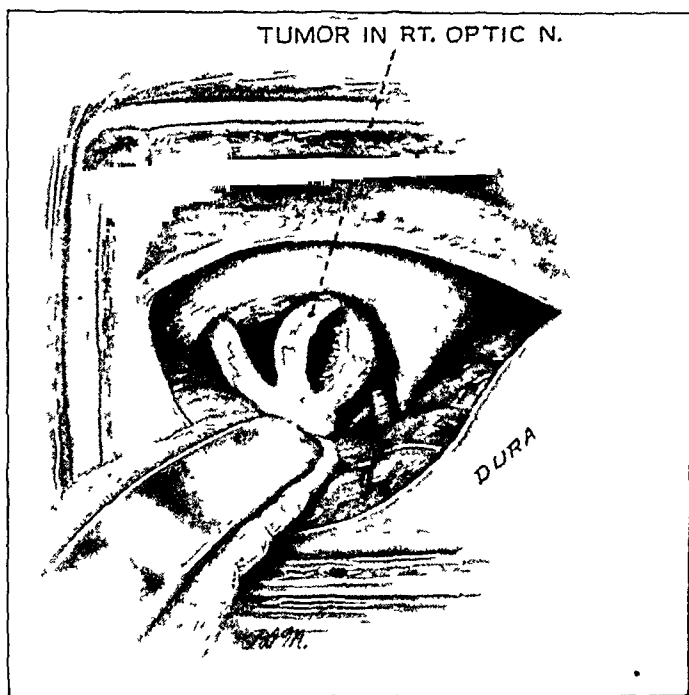


Fig. 13 (case 3).—Sketch of tumor, as seen at operation.

An encephalogram, made on October 23, revealed an essentially normal condition. There were no pathologic changes in the sella turcica. Complete studies of the urine and blood, including the Hinton test, revealed nothing abnormal. Lumbar puncture showed an initial pressure of 140 mm. of water; the fluid was clear and colorless, and the dynamics were normal. The total protein content of the spinal fluid was 40 mg. per hundred cubic centimeters. The Hinton and Wassermann reactions of the spinal fluid were negative. In view of the history and laboratory and clinical observations, a tentative diagnosis of tumor of the optic nerve was made.

*Operation.*—On October 27, a right frontal craniotomy was performed. The right frontal lobe was retracted, and the region of the right optic nerve was brought into view. Notes made by one of us (G.H.) concerning the operative observations were as follows: "It was at once apparent that the right optic nerve was greatly enlarged and somewhat red as compared with the left nerve, which was of normal size and contour. No tumor appeared between the nerves; there-

fore, it was fairly obvious that the enlargement and swelling of the right optic nerve represented a tumor of the nerve itself [fig. 13]. The nerve sheath was incised, and the tumor tissue was removed with a pituitary spoon. The growth extended backward into, or almost into, the chiasm, so that it was not feasible to resect the nerve at its junction with the chiasm, as I had at first hoped to do. The operation, therefore, was left as an intracapsular evacuation of tumor from the substance of the right optic nerve."

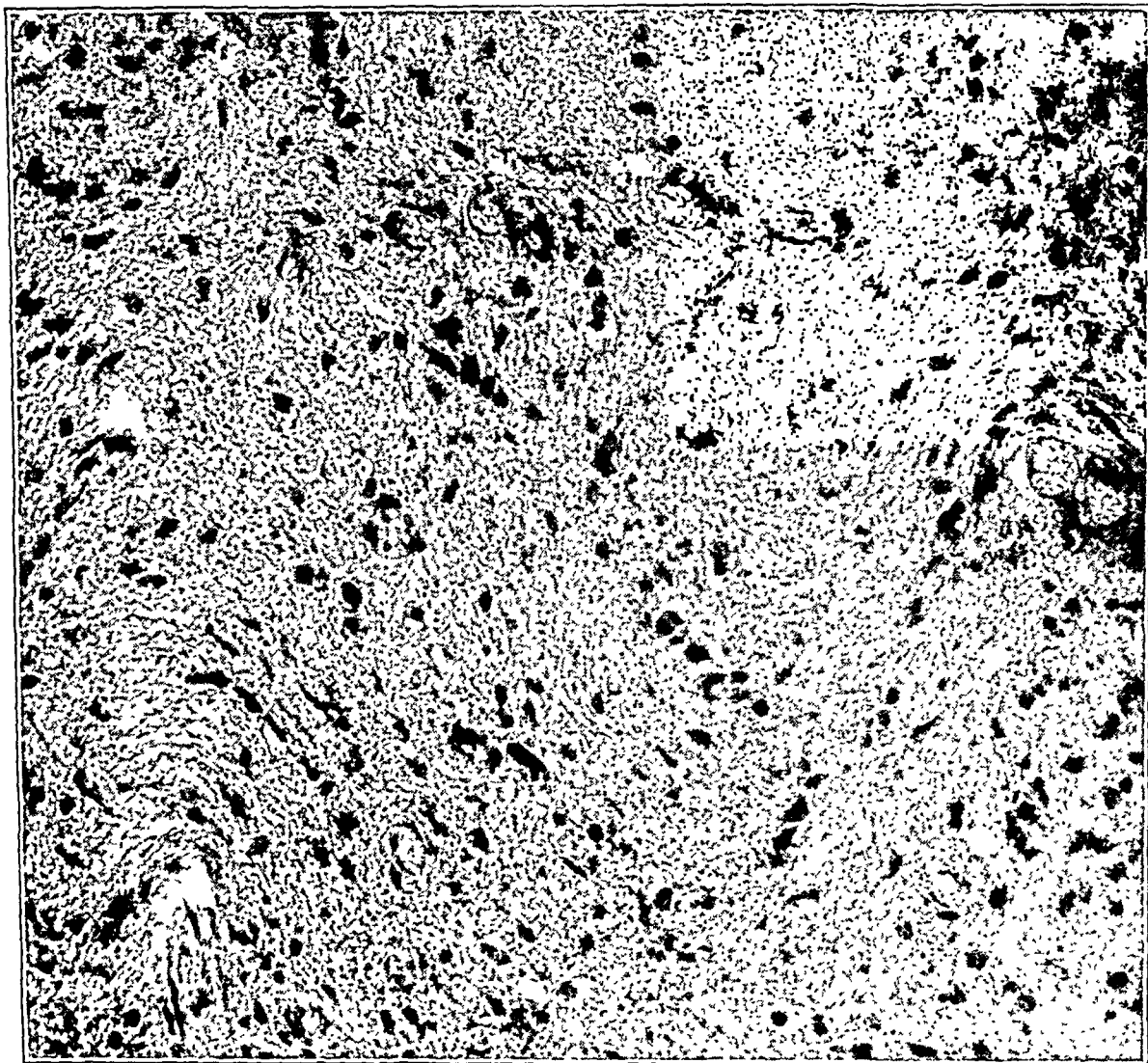


Fig. 14 (case 3).—Photomicrograph of tumor, composed chiefly of fibrillary astrocytes;  $\times 350$ .

*Pathologic Report.*—The tissue was composed mostly of astrocytes, separated by a fibrillary ground substance. An occasional large vesicular astrocyte was noted. With the phosphotungstic acid hematoxylin stain, the presence of these glial fibrils was confirmed. This increase in glial fibrils and astrocytes and lack of much evidence of degeneration were consistent with the diagnosis of a fibrillary astrocytoma (fig. 14).

The patient did extremely well after operation and was discharged on the thirteenth postoperative day. Five months later (April 9, 1942) she reported for examination. She still showed slight exophthalmos of the right eye (fig. 15), and vision was unchanged.

The patient returned April 27, 1946 (four and one-half years after operation) for another examination. She was getting along extremely well and had no complaints other than the blindness of the right eye. She had been married during the past year. The right fundus was pale, and about 1 to 2 D. of protrusion was still present. The slight exophthalmos on the right measured the same as before operation. Visual acuity and visual field in the left eye were nearly normal (fig. 16).

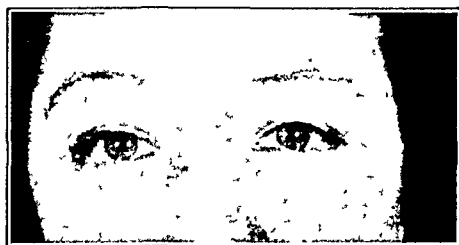


Fig. 15 (case 3).—Photograph of patient five months after operation, showing slight exophthalmos of the right eye, as before operation.

*Comment.*—As with our other 2 patients, this woman's chief, and practically only, complaint was the progressive visual failure in one eye, ending in blindness. In view of the lack of other evidence of the more usual conditions in the suprasellar region, and because of blindness in one eye with a normal field and normal acuity in the other, a preoperative diagnosis of a tumor of the intracranial portion of the right optic nerve could be made with a fair degree of certainty.

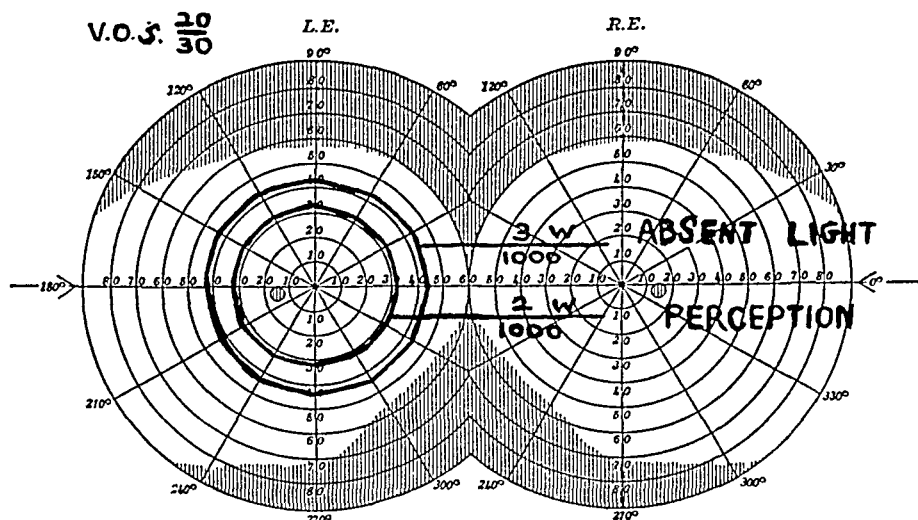


Fig. 16 (case 3).—Visual fields and acuity four and one-half years after operation (April 27, 1946).

One other clinical feature should be noted, namely, the appearance of the right optic disk. The enlargement was thought at first to represent unilateral papilledema; but later, when all the other features, including normal spinal fluid pressure and encephalographic abnormalities were taken into consideration, it was apparent that the protrusion of the

right disk was due doubtless to an extension into it of the presumed glioma, since before operation such a growth was thought to be most likely. It is likewise interesting that this protrusion before operation was measured as 4 D., whereas at a check-up examination by the same examiner (G.H.) five months after operation, April 9, 1942, this protrusion had receded to 1 to 2 D.

#### GENERAL COMMENT

Obviously, one is not justified in drawing far-reaching conclusions from so few cases as are here reported. However, these 3 cases serve well to emphasize that the prognosis of intracranial tumor of the optic nerve is not uniformly hopeless. Nor would it be fair to judge that the prognosis is as good as the report in at least 2 of these cases seems to indicate. The significant fact is that all patients with a verified lesion of this type are not faced with fairly rapid and completely bilateral loss of vision and may survive for an indefinite period, with perhaps only their unilateral visual defect to handicap them.

Visual failure in cases of chiasmal tumors, however, may be steadily progressive within a few months. The patient is often blind in one eye by the time a specialist is consulted, and vision in the other eye may be considerably impaired. It is interesting to note, however, that in the 3 cases reported here visual acuity in the unaffected eye remained good.

The fundi of all 7 cases reported by Martin and Cushing revealed atrophy of the optic nerve. In 5 of these cases it was definitely primary in type. In only 3 of 118 cases of intracranial tumor of the optic nerve reported by Hudson were the fundi normal. Instead of optic nerve atrophy, a certain number of the patients will present a fundus which resembles that of optic neuritis or early papilledema. The latter picture is sometimes difficult to distinguish from actual spread of the tumor into the globe in the region of the nerve head. However, such a distal spread of the tumor is said to be rare. Our case 3 is apparently an example of this feature. The normal spinal fluid pressure and the normal fundus in the opposite eye in this case support such an impression.

Association of neurofibromatosis with a tumor of the optic nerve has been noted on several occasions and was dwelt on in great detail by Davis.<sup>5</sup> An intraneural or extraneural growth of the optic nerve in such cases may well be a part of the underlying condition causing disseminated neurofibromatosis. In cases of obvious Recklinghausen disease one should be alert to the possibility that neurofibromas or other tumors may arise wherever there are nerve tissues. The optic nerve is not immune.

It should be remembered that a patient with a tumor of the optic nerve, apparently confined to the orbit or the portion of the nerve just



posterior to it, may harbor a neoplasm that usually spreads intracranially. The prognosis of such a growth is not so hopeless as it was formerly believed. Embryologically, it is in fact a tumor of the brain. The extraneural tumors of the optic nerve, like the meningiomas, can be cured by their removal. The patient with an intraneural tumor of the optic nerve, like a glioma of the brain, can be helped perhaps for a few years, and sometimes much longer. The ophthalmologist and the neurosurgeon, by coordinating their efforts in the treatment of these patients, can do much to prolong life and preserve remaining vision.

#### SUMMARY

Tumors of the optic nerve were classified by Verhoeff as intraneural (gliomas) and extraneural (meningiomas or endotheliomas). In addition to these two types, Hudson described a condition which he designated as fibromatosis. Case 2 reported here would seem to fall into this category.

Any type of tumor of the optic nerve may spread intracranially or intraorbitally or in both directions.

Failure of vision in one eye combined with some degree of exophthalmos, together with a normal visual field and visual acuity in the other eye in a patient showing no other evidence of an intracranial lesion, should speak strongly for the diagnosis of a tumor of the optic nerve within the skull.

Three cases of intracranial tumor of the optic nerve with survival from four and one-half to twelve years are reported.

The prognosis for patients having these tumors is not as consistently poor as is the general belief.

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Dr. M. T. Trumbull and Dr. W. A. Meissner, of the department of pathology of the New England Deaconess Hospital, described and interpreted the microscopic sections of these tumors.

605 Commonwealth Avenue.

# News and Notes

EDITED BY DR. W. L. BENEDICT

## GENERAL NEWS

**The Albert D. Frost Memorial Library.**—The department of ophthalmology of the Ohio State University College of Medicine, Columbus, Ohio, announces the opening of the Albert D. Frost Memorial Library, following Mrs. Frost's gift of her husband's ophthalmologic library. Plans for a study room in connection with the library in the new medical center are being made. To maintain the library, an endowment fund is needed, and an appeal is made to Dr. Frost's friends and others who might be interested in this worthy undertaking. Contributions of \$5 to \$25 are solicited. Checks are to be made out to the Frost Memorial library and sent to Arthur M. Cullen, M.D., University Hospital, the Ohio State University.

**Albrecht von Graefes Archiv für Ophthalmologie.**—This journal has resumed publication under the editorship of E. Engelking, W. Löhlein, O. Marchesani and K. Wessely. It is to be published by Springer Verlag, Heidelberg and Berlin, and J. F. Bergmann, Munich.

## SOCIETY NEWS

**Ophthalmological Society of the United Kingdom.**—The annual congress of the Ophthalmological Society of the United Kingdom was held on April 8, 9 and 10, 1948, with A. J. Ballantyne, M.D., LL.D., president, presiding. The program consisted in a discussion of "Subjective Disorders of Vision" (excluding those due to local ocular diseases), which was opened by Prof. H. Cohen, Dr. Denis Williams and Mr. J. H. Doggart. The Bowman Lecture for 1948 was delivered by Prof. Marc Amsler, of Zurich, Switzerland, on "New Clinical Aspects of the Vegetative Eye."

The following papers were presented: "Ocular Palsies Due to Infection of the Nasal Sinuses," Dr. Helen Dimsdale and Mr. D. G. Phillips; "Preliminary Survey of Forty-Five Consecutive Cases of Congestive Glaucoma," Mr. J. P. F. Lloyd; "Conjunctival Nevus and the Neurogenic Theory of Melanoma," Mr. Eugene Wolff; "Venous Pressure in Glaucomatous Eyes," Dr. T. L. Thomassen; "Observations on Clinical Perimetry," Dr. G. I. Scott; "Two Cases of Special Interest: (a) A Subconjunctival Rupture of the Globe with Extensive Migration of Uveal Pigment, and (b) Aneurysmal Varix of the Retina," Mr. G. T. W. Cashell; "Papilledema Associated with Toxic Hydrocephalus," Mr. A. G. Cross; "Latent Nystagmus," Mr. T. Keith Lyle; "Classification of the Unassociated Dystrophies of the Fundus," Prof. Arnold Sorsby; "Prognosis in Detachment of the Retina," Mr. C. Dee Shapland; "Mode of Development of the Vascular System of the Retina, with Observations on Its Significance for Certain Retinal Diseases," Dr. I. C. Michaelson; "Atropine in the Treatment of Glaucomatous Iridocyclitis," Prof. W. H. Melanowski. A film, "Autoversion of the Upper Lid (left), Voluntary, Unaided," was shown by Dr. W. C. Souter, and two pictorial demonstrations were made: "(a) Spasm of the Central Artery of Retina; (b) Entropic View of Retinal Vascularization; (c) Hypophysial Tumor Causing Homonymous Hemianopsia; (d) Hypophysial Tumor Causing Paralysis of the Third Nerve, and (e) Depigmentation of Iris in Chronic Glaucoma," Dr. H. M. Traquain, and "(a) Pressure Grafting in the Contracted Socket; (b) Epibulbar Dermoid Before and After Operation, and (c) Gummatous Ulceration of the Eyelids," Dr. J. Ellison.

# Society Transactions

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EDITED BY DR. W. L. BENEDICT

AMERICAN OPHTHALMOLOGICAL SOCIETY

John W. Burke, M.D., *President*

Walter S. Atkinson, M.D., *Secretary-Treasurer*

*Eighty-Second Annual Meeting, San Francisco, June 26, 1946.*

**Cataract Complicating Glaucoma.** DR. BERNARD SAMUELS, New York.

This paper was published in a previous issue of the ARCHIVES (38:353 [Sept.] 1947).

## DISCUSSION

DR. J. L. MCCOOL, San Francisco: One of the most important decisions the ophthalmologist must make is to know when to tell the patient of the presence of a cataract and how much to tell him. Eventually, in the vast majority of cases, simple chronic glaucoma will be complicated by opacities in the lens.

In the case of a young person with a clear lens, one should say nothing until opacities develop and then tell the patient frankly of the outlook. Before operating for glaucoma, it is best to tell the patient that he has a complicating disease which will eventually require further operation.

If the opacity in the lens has developed to a point where it is the major factor in the reduction of vision, I have combined a tension-reducing operation with extraction of the lens. A large conjunctival flap, such as is used in trephining, is laid down to the limbus, or moderate splitting of the cornea is carried out. A wide corneal incision is made with a Graefe knife, and a large scleral flap is made when the incision is completed. A number of small bites are then made in the scleral flap with a Berens forceps; a broad, deep iridectomy is performed, and the cataract is removed in its capsule.

**Development of the Ectodermal Framework of the Optic Nerve, with Especial Reference to the Glial Lamina Cribrosa.** DR. HENRY C. HADEN, Houston, Texas.

The author showed a series of fifteen slides made from photographs of sections of human embryos and fetuses illustrating the development of the ectodermal framework of the optic nerve and the formation of the glial lamina cribrosa. At about the 15 mm. stage the undifferentiated epithelial cells in the wall of the optic stalk are stimulated by the entrance of the optic nerve fibers into the stalk to change into glial cells, which constitute the framework of the optic nerve. At the 67 mm. stage mesoderm begins to grow into the nerve from the anlage of the pial sheath and replaces most of the glial cells, forming the definitive fibrous connec-

tive tissue septums of the optic nerve. The lamina cribrosa is formed by the ingrowth of fibrous connective tissue from the sclera, and thus forms the lamina scleralis. The portion of the nerve anterior to the lamina scleralis remains ectodermal, and this portion is called the glial lamina cribrosa.

**Mercury in the Lens (Hydrargyrosis Lentis).** DR. WALTER S. ATKINSON, Watertown, N. Y., and DR. LUDWIG VON SALLMANN, New York.

A rose-brown homogeneous reflex from the lens which occurs in persons who have worked with mercury a long time or have chronic mercurialism was discussed and studied. Sections of the lens processed by Christeller's stannous chloride fixative showed black and dark brown deposits.

The mercurial nature of these deposits was confirmed by additional microchemical tests, as well as by spectrographic determinations. A case was reported.

**Evaluation of Methods and Results of Cataract Operations as Performed in Private and Clinic Practice at Stanford University Hospitals.** DR. HANS BARKAN, San Francisco.

The author reviewed his method of cataract extraction in 584 extracapsular and 187 intracapsular operations on so-called senile cataracts in the previous five years. The visual results in both types were recorded, as well as the incidence of postoperative complications. The author expressed the belief that a cataract operation involving a relatively short period, with the absence of sutures unless really indicated, a minimum of traumatic manipulation and careful consideration in each case as to whether the visual result desired will be obtained as well with the intracapsular method has in the long run obtained a satisfactory percentage of useful and satisfactory vision.

The author uses the Viennese school of cataract extraction except that the speculum is employed to hold the lids apart, akinesis is included and sutures are placed in the superior rectus muscle in all cases and retrobulbar injection is used in practically all intracapsular operations and in few of the extracapsular operations. Two corneoscleral sutures are used in all cases of intracapsular extraction but in few cases of extracapsular operation. The operator sits at the right side of the patient and operates with either hand. The Graefe knife is used. The Hess shovel is used to remove debris. A total iridectomy is done in 20 per cent of extracapsular extractions.

**Keratitis Due to Cephalosporium.** DR. ARTHUR J. BEDELL, Albany, N. Y.

The second case on record of infection of the cornea with a species of *Cephalosporium* is reported. The corneal ulcer was the result of an abrasion caused by a cow's tail. The first laboratory reports implicated *Staphylococcus albus* and a few gram-positive cocci. However, sulfathiazole and penicillin were ineffective; and, since the author suspected a mold, treatment with potassium iodide was instituted, with satisfactory regression and subsequent culture of the cephalosporium. Photographs were included.

## Healing of Corneal Wounds: II. Variations in Adhesive Power of Fibrin in *in Vitro* Studies. DR. ALBERT L. BROWN and DR. FRANK A. NANTZ, Cincinnati.

The remarkable tenacity with which corneal wounds are sealed in the rabbit suggested the employment of fibrin in the repair of corneal wounds in man, for such natural formation in the aqueous of man is practically nonexistent. To this end, the role of fibrin in the cycle of corneal healing in the rabbit and dog was studied *in vivo*, as reported in the first paper on this subject. The present paper deals with *in vitro* experiments. In the living rabbit, fibrin seals a corneal wound mechanically until fibrosis can become established. It is difficult to determine exactly when fibrinolysis begins, but *in vitro* maintenance of a constant level with a gradual loss in adhesive power over eight days demonstrates the mechanical course outside the body. It was found that plasma and platelets in the human wound lend adhesive power to the edges of the wound.

### DISCUSSION

DR. THEODORE L. TERRY, Boston: The work on this subject with which I am familiar, relating largely to problems of war wounds, has not adapted itself to ocular injuries in practical ways. The fibrin film produced by Cohn and associates is not easily stitched into place, and the sutures pull out easily. Cohn's skin grafting unit, however, is of considerable interest. Solutions of fibrinogen and thrombin are readily made by adding a saline solution to the dry preparations. The one is painted on the raw under surface of the skin to be grafted, and the other is painted on the bed of the graft. Fibrin is formed when the graft is placed in its bed, thus obviating the necessity of stitches. It has a use in plastic operations on the lids.

DR. ALBERT L. BROWN, Cincinnati: We are not sure of the exact use as yet.

## Treatment of Staphylococcic Corneal Ulcerations with Antitoxin.

DR. JAMES H. ALLEN, Iowa City.

Corneal lesions occurring in the course of staphylococcic blepharoconjunctivitis are of two types: (1) superficial punctate epithelial keratitis and (2) marginal corneal ulceration with underlying stromal infiltration, iritis and occasionally progression to a ring ulcer. In 25 cases of the second type staphylococcus antitoxin was given and the only additional treatment was instillation of a 0.2 per cent aqueous solution of scopolamine hydrobromide for photophobia. A rapid response was obtained, furnishing clinical proof of the theory that toxin is an important factor in the production of this lesion. The administration of staphylococcus toxoid caused recurrence in 3 patients.

Since antitoxin therapy is of transitory effect, it is of practical value only in cases of severe staphylococcic infections in preventing permanent and irreparable damage to the cornea and should be followed by active immunization, chemotherapy or antibiotic therapy. It should also be useful in severe infections caused by penicillin-resistant strains. Serum sensitivity tests must be made.

Illustrations were given.

## DISCUSSION

DR. WILLIAM H. CRISP, Denver: An injection of typhoid and paratyphoid U.S.P. containing 20,000,000 or 25,000,000 organisms was given a girl aged 18 during an acute attack of conjunctivitis, with great swelling of the lids, severe swelling of the bulbar conjunctiva and a great deal of discharge; the condition had been resistant to penicillin given intramuscularly four times a day for two days. From the beginning, the reaction to the typhoid and paratyphoid vaccine was remarkable, and the eye was practically restored to normal in twenty-four hours. Some older methods may at times be just as good as, or even better than, the modern methods.

DR. ALEXANDER E. MACDONALD, Toronto, Canada: There is a vogue in ophthalmology, as well as in other medical specialties, to follow antibiotic treatment, to the exclusion of the older methods of therapy. I think I was the first to report the value of toxoid, and I wish to congratulate Dr. Allen on calling attention to the great value of this method of therapy.

DR. JAMES H. ALLEN, Iowa City: Typhoid therapy is of considerable value in the treatment of conjunctival and corneal lesions. However, in a case in which the globe was lost typhoid therapy was used but the lesion was not controlled. Treatment with antitoxin will control the acute manifestations rapidly, but the patient has to have a long series of injections.

**Value of Corneal Peeling or Corneal Resection in Ophthalmology.**

DR. GEORGE L. KILGORE, San Diego, Calif.

A summary of the historical methods of medical and surgical removal of corneal scars and opacities was given. The author uses the technic for corneal resection suggested by Weiner and Alvis except in cases in which the corneal tissue is to be resected for one half or more of its thickness. In these cases, he found that there is less danger of damage to the posterior corneal lamellae if isotonic solution of sodium chloride is first injected along the line of initial incision. Preoperative and postoperative management was described in detail. Scars and opacities can be removed with relative safety, especially if they lie in the superficial layers of the stroma. Visual improvement compares favorably with the results of keratoplasty when scars are superficial and a donor is not necessary. Aphakia is not a contraindication. Resection is the operation of choice in cases of certain dystrophies, recurrent extensive pterygium and symblepharon and a cornea with a small transparent area when keratoplasty is not advisable. Disfigurement of the eye by a reflex from a white corneal scar can be lessened by the replacement of superficial layers with transparent tissue. Irregular scars subjected to repeated ulceration can be removed, with relief of symptoms.

Three cases were reported.

## DISCUSSION

DR. CONRAD BERENS, New York: I wish to confirm the statements concerning the practical value of this operation. For about twelve years I have been performing a similar keratectomy. At first I tried simple excision with a cataract knife, with good results, but later found that in introducing the knife the heavy side made a deeper incision on one side than on the other. A knife was made for me by V. Mueller & Co., hol-

low ground on one side and curved on the back, which produced smoother scars.

I have been unable to determine whether there was less corneal scarring with the use of air injection, either in the rabbit or in the human eye.

Concerning results, I should like to mention a case of corneal scarring from a chemical burn in which I performed a superficial keratectomy after the method I mentioned and obtained 20/100 vision. This man had a seriously damaged eye, and I had to perform a deep excision, and even perforated the cornea. Later, I thought perhaps better vision might be obtained with a corneal transplant. Secondary glaucoma developed, however, and it was finally necessary to remove a cataract, which was probably traumatic in origin. Final vision was only 5/200.

There are many complications from corneal transplantation which make one hesitate in employing it. In a case of corneal dystrophy removal of the superficial layers of the cornea resulted in secondary scars, with only slight, or no, visual improvement. In a selected case I prefer to remove the superficial layers of the cornea by some method rather than perform a corneal transplantation. I have had troublesome complications from superficial keratectomy in only 2 cases—in 1, the development of a small central, superficial, painful capillary angioma after keratectomy for a burn of the cornea with steam, and in the other, a sensitive, superficial vascularized lesion in a man with recurrent keratitis of undetermined origin.

DR. GEORGE L. KILGORE, San Diego, Calif.: The results of this particular operation, are, of course, dependent on a clear cornea, and, as I brought out in the paper, I believe any diffuse scarring of the cornea with involvement of the deeper layers is a contraindication to an operation of this type. I believe that in those circumstances the prognosis for good vision is poor.

### **Pigmentation of the Palpebral Conjunctiva Resulting from Mascara.** DR. ALGERNON B. REESE, New York.

Six cases of pigmentation of the palpebral conjunctiva in women from 31 to 55 years of age were described which was thought to be due to the use of mascara or similar pigment-bearing cosmetics. It was concluded that some personal factor determines the occurrence of the lesion. The condition appeared as a granular, stippled pigmentation under the palpebral conjunctiva of both upper lids occurring as a narrow line at the upper border of the tarsus. The color varied from black to dirty light brown. Folliculosis was always associated. There were only mild symptoms.

Five excellent illustrations were shown.

### **Diagnosis of Early Glaucoma.** DR. HENDRIE W. GRANT, St. Paul.

In the presence of symptoms of unrelieved asthenopia, subnormal or unequal accommodation, a variation of more than a few millimeters in the tension of the two eyes, sclerosis of the nucleus of the lens or a history of glaucoma in the family, one should institute a searching examination for evidence of early glaucoma. Contraction of the peripheral fields and cupping of the optic nerve are late symptoms. Although the ocular

tension may be found to be normal on routine determination, enlargement of the blindspot is present if the tension has been recently elevated.

The author presented data in 27 cases of increased intraocular pressure without evidence of cupping of the optic nerve or changes in the peripheral fields; 1 case of slight cupping with increased tension found on only one occasion, in the early morning, and characteristic changes of glaucoma; 2 cases of acute congestive glaucoma with the fellow eye showing a shallow anterior chamber, normal tension and enlargement of the blindspot, and 3 cases of enlargement of the blindspot and symptoms suggestive of glaucoma but without evidence of increased intraocular tension.

#### DISCUSSION

DR. WALTER W. WRIGHT, Toronto, Canada: Dr. Grant has covered the scientific aspect of the early diagnosis of glaucoma. But we must not forget that we are physicians as well as scientists. Three patients whom I saw recently had all, I felt, been made much worse by having had a diagnosis of early glaucoma and had been greatly worried about it.

DR. RALPH I. LLOYD, Brooklyn: Von Graefe classified glaucoma under three types: acute glaucoma, chronic glaucoma and excavation of the disk with amaurosis. He stated further that hardness of the eyeball, excavation of the disk and displacement of the vascular stalks often develop before demonstrable changes in the field. Hoffman, of the Donders clinic, stated that "contraction of the fields occurs in all forms of glaucoma, but in glaucoma simplex it is not the first symptom."

Much the same problem exists today. There is little likelihood that cupping or elevation of tension will be overlooked. Field work is subjective and is held by many in low esteem, but the importance of its use should be emphasized.

Some patients who have had refraction at regular intervals will show cupping of the disk but not changes in their visual fields or increase in tension. After several years typical field defects may develop, but the tension will remain well within normal limits. Late in the course of the disease the tension may rise, but the condition in some patients goes on to blindness without increase in tension. In the cases with delayed or no rise in tension, there is not much hope of improvement. In the cases in which there is no rise of tension, the condition is probably not glaucoma at all but is due to pressure of sclerosed portions of the circle of Willis or to isolated patches of sclerosis in the nerve trunk, as shown by Fuchs. Some authors have claimed that in cases of the latter types the rise in tension occurs in the early morning, or at other times of the day, and may escape detection. Some assert that in these cases the glaucoma may be tested for by producing a sudden increase in blood pressure by having the patient drink water or plunge an arm into hot water and then into cold water.

DR. PETER C. KRONFELD, Chicago: Some of the enlargements of the blindspot described by Dr. Grant are of the order of the Seidel sign, and therefore of great diagnostic significance. Enlargements due to the addition of crescent-shaped areas laterally are more difficult to interpret, especially if the development of the tissue bordering on the nerve head is not typical.

I agree with Dr. Grant that a definitely glaucomatous defect in the visual field is of greater diagnostic significance than the actual observa-



tion of an elevated ocular tension on one occasion, because the glaucomatous field defect is indicative of many periods of increased ocular tension. That it takes many early morning periods of slightly increased tension to produce the earliest demonstrable changes in the field may be learned from observations on low tension glaucomas, which are refractory to miotics.

The actual equipment for tonometry is at its lowest point. However, new tonometers are soon to be available which will conform to the specifications for Schiötz tonometers, as stipulated by the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology.

The consistency of the reading obtained with the Gradle tonometer was much lower than that of readings obtained with most Schiötz tonometers, probably because the Gradle instrument has a foot plate curvature of 9 mm., whereas that of the Schiötz tonometer is 15 mm. The latter, moreover, produces a similar deformation of all human corneas (except pathologically flat ones), whereas the Gradle instrument deforms only the more strongly curved ones.

When accurate and durable tonometers become available, tonometry will come into its own again and will probably become the most valuable single means in the diagnosis of the glaucomas.

DR. HENDRIE W. GRANT, St. Paul: As Dr. Wright said, it is possible that a patient might have a neurosis following the diagnosis of early glaucoma provided he were not properly managed. I have not seen any instances in which the neurosis persisted if the patient was properly advised as to his condition.

In addition to the cases cited, there were 2 instances of shallow anterior chamber with enlargement of the blindspot but no elevation of tension, as well as 3 cases with early symptoms of glaucoma, an enlarged blindspot but no increase of tension. The latter type presents a really difficult problem.

Use of a mydriatic not only may fail to produce an increase in pressure but may actually cause a reduction of pressure. This is true in some cases of deep angle glaucoma.

### **Chemical Natures of the Aqueous Humor in the Glaucomas.**

DR. PETER C. KRONFELD, Chicago.

In the normal eye, as well as in the eye affected with deep chamber glaucoma, the ascorbic acid level of the aqueous is dependent on that of the blood. Determinations of the ascorbic acid content of the aqueous have failed to throw light on the mechanism of deep chamber glaucoma.

No relation was found in normal controls between the ascorbic acid level and the protein content of the aqueous. There appears to be a relation between the intraocular pressure and the protein content of the aqueous in the sense that at the higher pressures the blood-aqueous barrier becomes more permeable.

In 2 cases which were investigated the glaucoma was unresponsive to miotics, and the values for ascorbic acid were low, leading the author to postulate that the combination of low vitamin C intake with unrelieved glaucoma of long standing may be conducive to low values for ascorbic acid in the aqueous.

## DISCUSSION

DR. THEODORE L. TERRY, Boston: Recently, my associates and I have tried to establish in various laboratory animals by quantitative measurements of ascorbic acid the time when the aqueous humor takes on the adult character, but the work was not completed early enough for presentation here. The change in the ascorbic acid level in relation to glaucoma appeared interesting. Could the reduction be an indication of the activation of a process which led to cataract formation?

DR. PETER C. KRONFELD, Chicago: I believe that ascorbic acid is the most suitable substance to define as the specific product in the adult aqueous, but proteins and ascorbic acid should be determined in the same specimen. In neither of the aforementioned cases with low ascorbic acid levels were there signs of cataract. Even if there were, that would not have led one to expect a low ascorbic acid level of the aqueous, since only mature and hypermature cataracts are associated with ascorbic acid values as low as those shown in these 2 cases of deep chamber glaucoma.

**Ophthalmology During the War and in the Future.** SIR WILLIAM STEWART DUKE-ELDER, London, England.

The distinguished ophthalmologist briefly reviewed the developments in ophthalmology during the war years and offered predictions as to the direction of future investigations. In ophthalmic surgery, technics of dealing with intraocular foreign bodies were revolutionized, and the ingenious Berman locator was devised. Concepts of the minute central localization of the visual functions were put on a secure observational basis. Novel and fruitful suggestions in the fitting of artificial eyes were made. In ophthalmic medicine, the greatest advance was made in chemotherapy. Knowledge of the optics of gunsights, range finders, periscopes, graticules and viewing and scanning devices; uses of goggles; problems of dazzle, scatter and haze, and, above all, of night vision and dark adaptation have increased beyond all bounds.

Real advances were begun in two lines of investigation: the study of the performance of the eye at high altitudes and that of the scotopic, or rod, fields. A microelectrode was devised which picks up and amplifies changes in potential of a single fiber in the optic nerve when a cone or rod is stimulated by light. With elaboration of these two technics, great advances should be made in knowledge of the mechanism of photo-reception.

New studies on the formation and circulation of the aqueous are being made. With the electron microscope and radioactive tracer elements, new studies on the physiology of various parts of the eye are in progress.

The author stated the opinion that ophthalmology is on the threshold of many important and far-reaching discoveries.

**Visual Disturbances Due to Digitalis.** DR. D. F. GILLETTE, Syracuse, N. Y.

A historical summary of the visual disturbances ascribed to digitalis was given, and 3 of the author's cases were presented. The visual disturbances recorded in the literature are flickering of light, occurring

early, followed by chromatopsia, which may be ushered in by an intense white appearance of light objects. These white objects often have a colored border, usually blue or lavender, which may later spread out and cover the entire object. In other cases, the objects appear to take on a yellow, orange or green color. Other disturbances found by various authors are indistinct, dim, disturbed or confused vision; headaches; amblyopia; nystagmus; mydriasis; diplopia, and conjunctivitis.

In the author's cases visual disturbances developed in each of two or more courses of administration of digitalis. The symptoms, which increased in severity for from twenty-four to seventy-two hours after withdrawal of digitalis, took from ten to fourteen days to disappear. In the first case there were flickerings of light, xanthopsia and dim vision, central retinopathy and a central scotoma; in the second case, blurred vision, pallor of the disks and a central scotoma; in the third case, xanthopsia, difficulty in reading and white, wavy lines.

#### DISCUSSION

DR. S. JUDD BEACH, Portland, Maine: I have had a number of patients who complained of blue vision from digitalis, but none were taking the drug when they reached me, so that I can add little to the information already received. I should like to ask whether there is any other reason that most of these patients are at such an advanced age, other than that vascular lesions are more likely to develop with old age and require digitalis; and whether there is any information on why so few patients in proportion to the vast number who receive digitalis complain of these peculiar symptoms.

DR. ALBERT L. BROWN, Cincinnati: Apropos of Dr. Beach's comment that so many patients are digitalized but comparatively few show any visual disturbances, I should like to suggest a warning against digitalization of patients with advanced glaucoma. In the last five years I have seen patients with advanced chronic glaucoma who have had early and severe reduction in vision from the use of digitalis. One of my patients, aged 65, in poor general health, who had had a successful bilateral trephination for glaucoma, was subsequently digitalized and in one week had rapid reduction in vision, from 20/30 to 20/60, in one eye. He stated that he had noted peculiar colors but had thought it was part of his ocular condition. After cessation of digitalization; vision returned to 20/40.

A woman aged 66 required heavy digitalization and immediately complained of chromatopsia. Administration of digitalis was stopped immediately, and vision returned at once. A second, milder, attempt at digitalization had the same results; so quinidine was substituted, with no further visual disturbances.

DR. D. F. GILLETTE, Syracuse, N. Y.: It is my belief that visual disturbances of digitalis origin are commoner than has been realized. They are commoner among patients of the older group, because these persons require the drug oftener. Then, too, in such patients sclerotic retinopathy is often already present. It will be interesting to check the tension in cases of visual reduction from digitalis, as suggested by Dr. Brown.

#### Ocular Changes in Acute Disseminated Lupus Erythematosus.

DR. FREDERICK C. CORDES and DR. SAMUEL D. AIKEN, San Francisco.

A case of acute disseminated lupus erythematosus in a woman aged 30 was presented. The patient was observed clinically for six months be-

fore the fatal termination of the disease. Examination of the fundus revealed cotton wool exudates with small, irregular hemorrhages, as well as flame-shaped hemorrhages. There was papilledema. The most striking feature was the vascular changes. The veins were dilated and irregular in caliber, with perivascular thickening and small, isolated thromboses in the venous branches. The arterioles showed a spotty, disseminated distribution of very irregular, localized narrowings. In some areas there was complete occlusion, associated with perivascular thickening. There was also arteriolosclerosis. The changes in the arterioles may have been only the manifestations of diffuse hypertensive sclerosis. Microscopic examination showed subintimal thickening and sclerosis of the arteriolar and arterial walls, with narrowing of the lumens, and scattered, widespread occlusive lesions of the vessels, but none of the changes in the intimal endothelium usually considered characteristic of the disease.

The authors stated that they did not regard any single lesion, or combination of lesions, as pathognomonic of lupus erythematosus but that so-called toxic retinitis is the most typical and frequent in cases of acute disseminated lupus erythematosus.

#### DISCUSSION

DR. L. F. PHILIP KOCH, New York: This has been a thorough review of the literature and is especially valuable because of the report on the ocular changes in this acute systemic disease. Additional detailed reports on the ophthalmoscopic findings should provide sufficient information to lessen the confusion now existing in the early clinical diagnosis of this disease. It is my opinion that constant reobservation of the fundi will reveal the earliest signs, which I believe may be pathognomonic.

In the case reported, the intraocular lesions were not observed until fourteen months after onset of the disease, and from that time until death, there were numerous findings which were not sufficiently clearcut to rule out the coexistence of systemic hypertension. The presence of the latter was confirmed at autopsy. Thus, the question arises whether this case more properly should have been considered as representative of the Libman-Sacks or the Sencar-Usher syndromes, since it is my opinion that at the beginning classic, or purely typical, acute disseminated lupus erythematosus is primarily a disease of the arteriolar and venous capillaries and that the morbid process slowly, but inexorably, extends more or less diffusely in a proximal direction.

The retinopathy, therefore, is essentially mechanical, and its variations depend on individual variations in tissue structure. These variations, when complicated by the ocular manifestations of systemic hypertension sequential to the visceral lesions in lupus erythematosus, will afford still greater difficulty in diagnosis unless the individual retinal lesions are studied minutely with reference to the entire retinal picture and are correlated carefully with the clinical picture as a whole.

DR. SAMUEL D. AIKEN, San Francisco: Since writing this paper, we have observed 3 additional patients ophthalmoscopically. Two are still under observation. One is a 17 year old girl, who has been followed fourteen weeks; the other is a woman aged 39, who has been observed four weeks. Both patients present strong clinical and laboratory evidence to support a diagnosis of acute disseminated lupus erythematosus. Except for mild dilatation of the retinal vessels, the fundi appeared normal.

The third patient, a woman aged 40, had one cotton wool patch and one small hemorrhage in the retina of one eye, and her condition was probably "toxic retinitis." The diagnosis was established by autopsy.

**Lipemia Retinalis: Report of a Case.** DR. FERDINAND L. P. KOCH and DR. PAUL S. STRONG, New York.

This paper was published in a previous issue of the ARCHIVES (38:310 [Sept.] 1947).

DISCUSSION

DR. GEORGE STUART - CAMPION, San Francisco: I should like to show "kodachrome" slides of the fundus of 3 patients with lipemia retinalis.

The first picture is that of the left fundus of a white man, aged 29, who, when he entered the hospital in coma, had 1,660 mg. of cholesterol and 15 Gm. of total lipids, per hundred cubic centimeters of blood. He was known to be diabetic and to have strayed from his diet. The entire fundus was pale; the creamy, cordlike vessel seemed to cast a shadow, and the arterioles were indistinguishable from the veins except for size. The pallor and the opaque appearance of the vessels were due, of course, to the heavy concentration of emulsified fat carried in the blood stream.

For the second patient, a white man aged 27, the blood cholesterol measured 885 mg., and the total fat of the blood 5 Gm., per hundred cubic centimeters. He did not know that he had diabetes. The lipemia in this case was not as pronounced as in the other cases and cleared rapidly, as it always does, under a diabetic regimen.

The third patient, a white man aged 30, was unaware of his diabetic state. At the time the first picture was taken, the blood cholesterol was 2,000 mg., the total fat of the blood 10 Gm. and the blood sugar 242 mg., per hundred cubic centimeters. The second picture, taken sixteen days later, showed definite improvement, but the fundus was still pale and the vessels were cordlike.

DR. ARTHUR J. BEDELL, Albany, N. Y.: I present one picture of lipemia retinalis sent me several years ago by Dr. Grady Clay.

DR. C. A. CLAPP, Baltimore: While this is the sixty-sixth reported case, there are many more unreported. I should like to draw your attention to another type of lipemia retinalis, which is not diabetic but apparently is a familial type. Hold and others, in 1939, reported the case of an 11 year old girl from Johns Hopkins Hospital who had repeated gastric crises, extending over several months, each being followed by lipemia retinalis. It was interesting that one of her younger brothers had lipemia and that the mother had an increased amount of fat in the blood. This case was studied carefully, and it was found that the fat increased after administration of lecithin, choline, thyroxin, insulin, liver extract or anterior pituitary extract. The only treatment other than regulation of diet which lessened the lipemia was blood transfusion. The lipemia was fairly well controlled with a low fat diet, and the latest report in this case is that the patient has gone along for several years and that the lipemia has been controlled fairly well with a low fat diet.

A recent case, not reported, is that of a 9 year old boy, in which the lipemia retinalis was discovered on routine examination and it was found that several members of his family had increased fat in the blood and 1 had slight lipemia retinalis.

**Dicumarol and Rutin in Treatment of Retinal Vascular Disorders.**

DR. ANGUS L. MACLEAN and DR. CHARLES E. BRAMBEL, Baltimore.

Twenty-one cases of various vascular retinopathies, including occlusion of tributary veins, partial occlusion of the central vein, diabetic retinopathy, degenerative retinopathy, central serous retinopathy (angiospastic) and Eales's disease, occurring in persons from 34 to 72 years of age, were treated with dicumarol and/or rutin. The dicumarol was used for inhibition of the thrombotic process, and the rutin, for decreasing capillary fragility. In this series of cases there was a definite decrease in the prothrombin clotting time of dilute plasma as compared with that of normal controls. Increased capillary fragility was present only in cases of idiopathic hemorrhagic disease (Eales's disease).

The authors expressed the opinion that the absorption of the hemorrhages in these diseases was decidedly more rapid than could have been expected in cases without treatment.

Photographs of the fundus are included.

**Pseudotumors of the Macula.** DR. RALPH I. LLOYD, Brooklyn.

The author reviewed and classified the various changes which simulate tumors of the macula, such as disciform degeneration of the macula, Coats's disease, senile and presenile macular degenerations, tuberculous lesions in young patients and idiopathic retinal detachment. The pathologic descriptions of these conditions, as well as several drawings, were included.

## DISCUSSION

DR. ARTHUR J. BEDELL, Albany, N. Y.: Six photographs of the fundus were shown to illustrate the need of critical consideration of all details—vascular, retinal and choroidal—in the diagnosis of lesions in the macular region.

Senile macular degeneration can, by means of these pictures, be traced from its inception to its termination as an organized, elevated gray mass. Care must be taken to recognize this condition as vascular rather than neoplastic.

DR. ALGERNON B. REESE, New York: A lesion belonging to this interesting group is one which arises from a massive intraretinal hemorrhage in the newborn, or as a result of trauma in early childhood. The organization of this hemorrhage leads to the formation of an elevated white mass, which may be confused with retinoblastoma. I have 12 cases of such a lesion. I reported several cases under the title "Massive Retinal Fibrosis in Children" (*Am. J. Ophth.* 19:576 [July] 1936).

In my opinion, the cause of this lesion is the same as that of a similar lesion which occurs in the brain; I refer here to the massive intracranial hemorrhage which occurs at birth and leads to the clinical picture of spastic paralysis. These conditions—massive intraretinal hemorrhage and massive intracranial hemorrhage—probably have the same causative factors. They stem from the same vascular system. An important etiologic factor is increased pressure in the jugular area, which is transmitted to the terminal vessels because there are no valves in the jugular area to diminish the force of this increased pressure. A contributing factor is perhaps the hypoprothrombinemia, which is known to be present during the first days of life.

DR. THEODORE L. TERRY, Boston: There must be some anatomic or physiologic reason that the lesion which Dr. Lloyd discusses is located in the macular region so frequently. It is possible, but improbable, that continuous, but subminimal, exposure to bright light is concerned. Reduction in vision often precedes visible pathologic change. Recently I saw a patient whose vision decreased from 20/15 to 20/30 in three weeks, but only on the third visit was edema of the macula visible.

The age of the patient helps to differentiate Coates's disease of the early decades of life and disciform degeneration of the third or later decades.

Angioma of the choroid gives a similar picture. This lesion may look like malignant melanoma clinically, but pathologic examination after enucleation may reveal nothing, as the choroid angiomas may have emptied and become invisible when the ocular vessels were severed. So far, my idea that angioma may be recognized by applying pressure to the globe to see whether the lesion disappears has not been tested thoroughly.

Careful measurements of the scotoma at intervals of a few weeks may show that the field defect is reduced in case of the so-called juvenile form of disciform degeneration.

#### **Experimental Studies on Retrobulbar Neuritis. DR. P. J. LEINFELDER and DR. W. A. ROBBIE, Iowa City.**

Because of many reports in the literature relating to the role of nutritional disturbances in retrobulbar neuritis and the possible association of cyanide poisoning, the authors subjected rats to a series of experiments in which diets were altered in various ways, and in various combinations of deficiencies of thiamine, the vitamin B complex and riboflavin, and in which the rats were fed a low protein diet and subjected to exposure to hydrogen cyanide gas.

In none of the experiments was significant degeneration in the optic nerves observed, even though the rats with deficiency in the vitamin B complex and those with thiamine deficiency were reduced to extreme degrees of malnutrition and were at the point of death at the time of the removal of tissue for examination. Conclusive evidence of injury to the ganglion cells was not obtained.

In an animal exposed to cyanide gas and made deficient in thiamine there was slight degeneration in the optic and sciatic nerves, but not enough, according to the authors, to warrant conclusions.

#### **The "Duction Test"—An Evaluation of the Various Technics. DR. WALTER H. FINK, Minneapolis.**

An analysis and evaluation of the commoner methods of testing ductions was made, and a plan was presented for a technic which is designed to secure more constant and dependable results. The author has tested 100 patients with 20/20 vision and a small refractive error, only patients with a small amount of heterophoria, normal accommodation and a normal near point of convergence being used. He recommended the use of the phorometer with rotary prism and the Snellen or rotating target, and he recorded the data for base-in and base-out prisms with both near and distant targets, measuring the blur-out, break and recovery points.

## DISCUSSION

DR. WALTER B. LANCASTER, Boston: Of the tests of the power of convergence and divergence, I learn more from the so-called duction test than I do from measuring the heterophoria with the Maddox rod. These tests show the capacity of the patient to overcome whatever deviation is present, and this is more important than to know the amount of deviation.

I object to the term "duction test." The power of abduction and adduction of one eye is measured by covering the other eye and having the uncovered eye follow a finger to the right and to the left. If both eyes are examined together and rotated to the right and to the left, dextroversion and levoversion are measured. The first is properly the duction test, and the second is the version test. Vergence is the power of convergence and divergence.

The term "duction" is a term authorized by the optometrists, and it is incorrect. The orthoptists correctly use the term vergence. That is what it is—convergence, divergence and vertical divergence.

To demonstrate the importance of vergence tests, take a case of exophoria: Suppose there are 6  $\Delta$  of exophoria for distance and 12 or 14  $\Delta$  for near vision. When one tests the divergence for distance, the patient will be able to overcome prisms up to perhaps 12 or 14  $\Delta$ , base in. His break point will be 12  $\Delta$  and his recovery point 11  $\Delta$ , or his break point will be 14  $\Delta$  and his recovery point 12  $\Delta$ . The difference between the break and the recovery point is very small, indicating that the reflex is working efficiently—in fact, is stronger than is needed. Then one tests the patient's convergence with prisms base out. One finds that he gets diplopia at, say, 10 or 12  $\Delta$  of convergence. One then turns back to see where he will recover, and it is not uncommon to find that he does not recover well, and that his convergence power goes down to 6, 4, 2 or 0  $\Delta$  before he recovers. Not only is his amplitude of convergence small, but even more striking is his poor recovery as the converging prism is reduced. This shows that the converging reflex is working poorly and calls for active training of converging power. This procedure is a test of the reflex produced by images on the retinas of the two eyes which cause diplopia. Winking stimulates fusion in a manner similar to Dr. Fink's moving target and may be used in this test.

The room should be light, and there should be a Snellen chart or a red star on the wall. The reason for having the room lighted is this: If one has only a spot of light, the stimulus is on the macula, whereas if one has the end of the room lighted one gets a stimulus not only to the macula but to the periphery; and, as Dr. Burian showed, the power of the periphery of the retina to stimulate fusion is great.

The exact results in these measurements are not of importance, but the relation of the deviation and the break point and the recovery point are extremely important.

DR. AVERY DEHART PRANGEN, Rochester, Minn.: Dr. Fink's theme, as he expressed it to me, is that he utilizes the entire visual mechanism—the field of vision as well as central macular fixation. Instead of using a spot of light, he lights up the whole target, so that he is attempting to adapt the test of lifelike conditions, with the whole target instead of a small spot of light. I agree with Dr. Lancaster on the use of the term "vergence" instead of "duction." When one thinks in terms of vergence,



I believe one has a different, and better, concept of this important function.

DR. THOMAS D. ALLEN, Chicago: The test of the ability to converge and to diverge the eyes is one not of turning ability but of two cerebral functions: fusional ability and the ability to overcome relatively difficult obstacles. These two cerebral functions are skills that are not always easily used but are readily acquired, just as are writing and skipping rope; and they are of great value to one who does a good deal of comparatively close work.

My colleagues and I have now revamped our methods of muscle testing and do Maddox rod and cover tests and determine the near point of convergence routinely; if the results with these tests are not quite within normal limits, the cover test is used in the six cardinal positions, and the relative stereoscopic ability is studied. If there is found with these tests a convergence or a divergence deficiency, some simple orthoptic home treatment may be suggested to, or even urged on, the patient.

For suppression or for situations requiring more extensive training, we send the patient to the orthoptist, who can spend the necessary time to explain in detail and to institute a training schedule. Occasionally we use the major amblyoscope ourselves, and often the "jump-deduction" stereoscopic pictures.

The tests at the near point should be carried out with the gaze depressed about 20 degrees, as in reading.

DR. CONRAD BERENS, New York: I find that many patients have difficulty with convergence. Dr. Fink used the rotary prism for making his studies and stated that he gets better results with it. One must decide what one means by better results. Twenty-five years ago, when we were working with the original Howe ergograph and used prisms for testing convergence, my associates and I realized that prisms introduced a factor which made our tests unreliable. We found it highly desirable to substitute a small dot or a line for prisms, and to take the near point of convergence repeatedly. Also, we found that taking the near point once or twice means very little. Dr. Fink emphasized that the test object to be used is of great importance. If a light is used, as is often done by my associates, because in using the Maddox rod they have the fixation light in their hands, and they report a near point of convergence of 70 mm. and a prism convergence for near vision of only 10 or 12  $\Delta$ , I suspect immediately what they have been doing. The studying of convergence with test type, as Dr. Fink brought out, brings us added knowledge of accommodative convergence.

I have never been pleased with rotary prisms. In the first place, when using a rotary prism in a phorometer, I find difficulty in seeing what the eyes are doing, which I think is most important. I prefer the prism rack or loose square prisms. The best method is to use one of the major stereoscopes to study fusional convergence against accommodative convergence. Also, in order to study convergence, a careful study of fatigue in convergence, and sometimes of divergence, should be made.

DR. WALTER H. FINK, Minneapolis: Undoubtedly, there are various methods of testing the vergence, but it seems logical that one method should be adopted; this would tend to eliminate much confusion, and one's results would be better interpreted by others.

**Surgical Treatment of the Extraocular Muscles.** DR. AVERY DEHART  
PRANGEN, Rochester, Minn.

The author reviewed and summarized his experiences in extraocular muscle surgery during a long career. He mentioned many of the new developments and called attention to errors made in the past by surgeons who operated on the muscles of the eye. He called attention particularly to the necessity of careful and accurate preoperative diagnosis, and he gave many practical and worth while suggestions as to operative and postoperative care.

DISCUSSION

DR. J. H. DUNNINGTON, New York: I am in complete accord with the plea against undue conservatism, especially after the diagnosis is made and the patient is in the operating room. One should study the case carefully, make an accurate preoperative diagnosis, decide on what has to be done and do it. I agree that in the vast majority of cases a general anesthesia is preferable. I also urge the adoption of Dr. Prangen's suggestion of adequate exposure. In the preoperative diagnosis, I personally believe that prismatic measurement of the deviation is an essential part. Repeated tests are essential.

I do not agree with the author with respect to large recessions. I favor a recession, as a rule, of not more than 3.5 mm., even on the external rectus muscle, and I do not believe that a tentotomy of the external rectus can be done with impunity, since complete paralysis or partial limitation of motility may be produced.

I, too, use surgical gut sutures routinely. I agree with him as to simple postoperative care and do not use anything but light protective dressings for a few days.

Although I wrote on the subject in 1929 (*Tr. Am. Ophth. Soc.* 27: 277, 1920), I never do a complete tenotomy of the inferior oblique muscle at its insertion without some form of scleral anchor, for I found that when this tenotomy was performed it produced a complete and permanent paralysis of the muscle. Recession or a myectomy at the origin of the muscle is the method of choice.

DR. CONRAD BERENS, New York: I must confess that I, too, exercised undue conservatism formerly, for about the same reasons as those given by Dr. Prangen. Another reason is that I became imbued with the idea that one should do something more with orthoptics than attempt to obtain functional, and not merely cosmetic, results, and I was most anxious to see what could be done. I found out I could not do more than the patient could do with the fusion at his command; but, until I had sufficient experience, I expected the patient to obtain better results than he could possibly obtain. Now I operate much earlier than I did, and I believe that this factor is important in getting better results.

The mention of overconservatism raises the question of how many muscles one should operate on. In cases in which more than four muscles were operated on and surgical gut was used, particularly chromic surgical gut, I have had some severe reactions. With the use of "nylon" or silk sutures my reactions have been much less pronounced. I operate frequently on three or four muscles at a time; perhaps with more accurate diagnostic methods in the future one will operate on more. Recently I have operated on as many as five at one time. I think that one should

divide one's surgical procedures between the two eyes whenever possible, and so avoid underaction in some cases, a result which may be due to trying to do too much to one muscle.

Congenital anomalies have been most troublesome, especially with the inferior oblique muscle.

In performing the retroplacement operation, I have freed the inferior oblique muscle from its scleral insertion.

The matter of diagnosis is becoming increasingly important, and technicians are writing that they have given orthoptic training to patients without relief. In their opinion, this is because in many instances spasm of the inferior oblique was not diagnosed.

One thing which Dr. Prangen did not bring up, far as I know, is the question of the fixing eye. I think the determination of fixation, not only in the primary position but also in the main diagnostic direction of gaze, is most valuable and should be a part of the preoperative record because of its great importance in determining what should be done surgically.

I know of no other test which has given me the accurate information, especially in the case of vertical deviations, which the screen and parallax test with prisms does. It is valuable and helpful, not only for diagnosis but also in the evaluation of postoperative results.

The clever idea of tying surgical gut sutures outside the conjunctiva, which Dr. Prangen suggests, I have not tried, but I have been using "nylon" sutures and have found them satisfactory. I have had a new suture developed by Davis & Geck, Inc., especially suitable for the inferior oblique muscle, or double-armed blue "nylon" (00000). The needle they have made is a little stronger and more curved, a feature which is important in operations on the inferior oblique.

With regard to resections of the lateral rectus muscles, I agree with Dr. Prangen as to the maximum amount, that is, 10 to 11 mm. When the inferior and superior rectus muscles are concerned, I agree that it is difficult to resect more than 5 or 6 mm. I do not make a recession of the medial rectus muscle of more than 3.5 mm., as I do not like to weaken convergence. When one speaks of the amount of recession, it is important to specify how the sutures are inserted into the muscle. If they are inserted 1 or 2 mm. from the free border, one may be making a recession of 1 or 2 mm. less than was intended. The perforated forceps I use brings the free edge of the muscle in apposition with the sclera, so that 3.5 mm. measures the amount of recession of the muscle.

With respect to recession of the lateral rectus muscle, I am also rather conservative; in cases of heterophoria I may do a recession of about 5.5 mm.; in cases of amblyopia, one of 7 or 8 mm.

In 97 cases of recession of the inferior oblique muscle on which I have accurate preoperative and postoperative data, the screen and parallax test with prisms showed that an average of 1 mm. of recession in the primary position produced 1  $\Delta$  of correction, both at 6 meters and at 25 cm. However, in some cases I found that a recession of the inferior oblique of 5 mm. caused no change in the vertical deviation; in other cases too much correction resulted, but I usually obtained a little less than the average correction.

DR. WALTER W. WRIGHT, Toronto, Canada: No mention was made of the age of the patients. My experience with patients with strabismus has been that my good results were obtained with young children under 4 years of age. With young children much less recession is needed. No child is too young to be operated on if the procedure is indicated.

DR. J. L. MCCOOL, San Francisco: I should like to discuss the technic of the recession which I use. It is a modification of Jamison's and seems to afford a more accurate means of determining the amount of the recession and a somewhat firmer attachment of the muscle stump to its new position.

After the muscle is isolated, the tendon is grasped with the Jamison forceps about 2 or 2.5 mm. from its insertion. The tendon is then cut as close to the sclera as possible, so that some of the fibrous tissue of the insertion is left on the end of the tendon fibers. This has a tendency to hold the tendon fibers together and to act as a buttress when the sutures are placed, binding the tendon to the sclera in its new position.

Three mild chromic double-armed 0000 sutures are then placed in the sclera, in a line parallel to the original insertion. These are then carried through the tendon anterior to the forceps and tied firmly. This method of suturing has two important advantages: a more accurate placement of the sutures in the sclera, and a firmer hold on the tendon, because the suture is tied across the long axes of the fibers and the binding of the fibers at their end helps to prevent any slipping.

The forceps which I show you digs down into what is left of the stump of the tendon and facilitates insertion of the sutures into the sclera by preventing rotation of the globe.

I take exception to Dr. Berens' statement of operating on so many muscles at one time, since the ideal is to preserve, create and educate ultimately the patient in binocular single vision. Many times a shortening of a superior rectus muscle in hyperesotropia will achieve parallelism without any further attack on the lateral rectus muscles.

DR. THOMAS D. ALLEN, Chicago: I want to mention a case on which Dr. James White consulted with me. The patient had a vertical diplopia, which gave him varying amounts of hyperphoria and exophoria in repeated tests and in the cardinal positions. No two of my findings were alike, and yet there was always more or less concomitant hyperphoria. The patient had been injured in a mine four or five months before I saw him. Dr. White stated that he thought the right eye was lower than the left and suggested that a small cartilage graft be placed under the right eye and the eye be raised. This we did. The patient now has normal vision, normal muscular balance, good fusion, no diplopia and almost no hyperphoria or exophoria, and he is extraordinarily happy; and we did not touch a single muscle.

DR. A. DEHART PRANGEN, Rochester, Minn.: In measuring the amount of recession or resection, I think all make about the same estimates but arrive at them in different ways. Perhaps what I call 5 mm. of recession or resection someone else, by his method of measurement, might estimate as more or less. The point I wish to make is that the surgeon makes enough recession or resection to accomplish his objective.

I believe that Dr. Dunnington was the first to advocate the posterior, or global, approach in operating on the inferior oblique muscle.

I was asked how long I keep my patients in bed after surgical procedures in the ocular muscles. I keep them in bed four to six days.

As to the age for muscle surgery, I have long since ceased to regard the age of the patient as of any importance in deciding when to operate or what to do, except that the child should be old enough to undergo a general anesthesia safely. Except for this factor, when the indications for operation are present, I should operate.

**Medical Assistance at Professional Level.** DR. PARKER HEATH, Detroit.

The author discussed the advisability of developing a professional group of ophthalmic associates and stated that such a group could be created within existing educational facilities. The suggested program would run four years at college level and lead to a bachelor's degree. About half the subject matter would lie in the field of the humanities and would be taught by the literary and scientific faculties. The remainder falls largely on the technical side and would be the responsibility of the medical teachers. The standards for admittance would be those of college level plus aptitude. The formation of this group would extend the present medical services and better the lot of the patient.

#### DISCUSSION

DR. CONRAD BERENS, New York: In the training of orthoptic technicians, my colleagues and I have been impressed by the need for this type of service. At first we took any applicant we were able to get; now we almost always insist on a college education as a requirement for admission, for we found that in physiologic optics, for example high school graduates were not able to understand the problems. I hope this idea of Dr. Heath's will receive the approval it merits and that a sufficient number of these technicians will be available soon.

Dr. Heath has pointed out that a sufficient number of ophthalmologists cannot be, and are not, trained. The only realistic approach to the problem of which I know is the Boston plan, which Dr. Lancaster and Dr. Beach are fostering.

DR. E. C. ELLETT, Memphis, Tenn.: Another subject closely related to this problem is the propriety of an ophthalmologist's taking an optometrist into his office for some of this other work which Dr. Heath has discussed, to be done, of course, under supervision.

DR. WILLIAM H. CRISP, Denver: The whole subject of the proposed degree and training will have to be coordinated carefully with the question Dr. Ellett has just raised, and also with the development of a special degree in orthoptics. In the long run, movements of this kind have results that one cannot foresee, as in the creation of a new professional class, or new professional classes, which will serve the public in competition with the medical profession. One might also consider the analogy between these movements and what exists in Russia, where there is a special class known as *feldshers*, who are trained in medicine, but on an inferior scale and for a shorter period, and who go out and do certain things in medical practice; and also in Germany, where there are two kinds of dentists, one who is limited as to the kind of work he can do, on a lower level, and another, the dental surgeon, who does the higher

types of work. I merely suggest that the present proposal requires broad consideration and should not lead to hasty action in the establishment of a degree for this purpose.

DR. PARKER HEATH, Detroit: Dr. Berens has long been a pioneer in teaching in this field and has been an inspiration to many who are endeavoring to broaden the scope of the practice of medicine without losing control of it.

We have, in the nursing field, given a special course in ophthalmic nursing, two hours of medical teaching, and the aftermath has been that our patients are better satisfied with certain forms of group nursing; it costs the patients less; they are given better care, and it has almost done away with our need of the special nurse.

In regard to the matter of risks suggested by Dr. Crisp, I believe the same warning was made about nurses and about orthoptic technicians. I think that the hazards and dangers are mostly imaginary, for the group is subject to medical laws and is taught about medicine and medical principles.

**The Dissatisfied Refraction Patient.** DR. C. A. VEASEY JR., Spokane, Wash.

The author discussed the problems presented to the ophthalmologist by the dissatisfied refraction patient. He reviewed the usual causes of complaint and included some unusual presenting symptoms. Emphasis was placed on the importance of giving the patient the necessary time to voice his complaints and on the necessity of locating the particular trouble and of correcting it or explaining irremediable difficulties.

#### DISCUSSION

DR. S. JUDD BEACH, Portland, Maine: I should like to emphasize some of the implications of this paper; as Scott Sterling has said, "Overcorrection is the besetting sin of the ophthalmologist." By this, I mean overcorrection not only in presbyopia but also in hyperopia and myopia. The ophthalmologist fools only himself when he imagines he is making his patients emmetropic. Certainly, he tries to find out what will make them emmetropic, but then he modifies that according to the circumstances. I presume it is the experience of every one that most myopic persons do not like to have a complete correction for distance; they usually prefer to wear a correction which will make objects around the room distinct. One reason for what people like to call "shading" a prescription is that every change in lenses produces a different size object and thereby alters the space perception. I have always assumed this to be one reason that it is so easy to give a child, for instance, one with squint, high correction and have it worn with perfect ease, when it is so difficult to give a similar correction to an adult. The adult has been accustomed to associate objects with a certain appearance and size, by which he places them in space, whereas the child has not become so fixed in his ideas. Each patient is an individual, and the prescription and refraction must conform to the patient, and not to the prejudices of the refractionist. The method of refraction should also be adapted to the patient.

Some patients are uncomfortable under fluorescent lighting, and in the office it is reenforced with incandescent desk lights.

Many patients have nothing the matter but a little anemia, or even a low grade fever which comes on in the afternoon, and that is when their eyes are tired.

The ophthalmologist should never forget to write down the visual acuity with the patient's old lenses in order that he may refute the occasional patient's statement that he could see better with his old glasses than he can with the new ones.

**Evisceration with Intrasceral Implant: A New Technic.** DR. C. S. O'BRIEN and DR. JAMES H. ALLEN, Iowa City.

The authors described a new technic designed to give a better appearance and better mobility to a prosthesis after evisceration. The method under trial involves the implantation of a "lucite" implant with a peg extending through a trephine opening in the cornea, the evisceration having been done through meridional scleral incision. The prosthesis is then attached to this peg.

DISCUSSION

DR. WILLIAM H. CRISP, Denver: I should like to ask whether there has been much tendency to foreign body reaction around the implant, and what is the longest time that any of the patients have worn the implant.

DR. WENDELL L. HUGHES, Hempstead, N. Y.: I shall describe here a new type of combined integrated implant and artificial eye. (The commentator then detailed a method of attaching the tendons of the rectus muscles and the fascia directly to a special implant, a removable external prosthesis attachment being then fitted on the implant. The contents of the eye are removed through an incision beneath the superior rectus muscle).

DR. JAMES H. ALLEN, Iowa City: I realize that in some cases the scleral implant would be lost and in other cases it would be contraindicated; so I have worked with muscle cone implants. The basic principle of design is that of Col. Norman Cutler, whose implant is a plastic ball in which a gold anterior portion is embedded. The metal part consists of a face with a square hole in it. From the margin of the face four arms extend outward to support a gold ring, to which the four rectus muscles are attached. We have varied the design in several respects, as may be seen in the slides. We use a round hole and have no difficulty with abnormal rotation of the prosthesis.

The muscle cone implant, in addition to the peg principle of Colonel Cutler, includes the groove principle of Wheeler's implant; however, we have added bridges across the grooves, a device which traps the rectus muscles and prevents the implant from slipping. The technic following enucleation consists in slipping the rectus muscles through the grooves and under the bridges. The ends of the muscles are split and the lateral and medial rectus muscles are overlapped and sutured together around the peg. The conjunctiva and Tenon's capsule are closed with a purse string suture, which pulls them down around the peg.

If the intrasceral implant fails, it is still possible to insert a muscle cone implant, as demonstrated in the accompanying moving picture. One of the advantages of direct contact between the implant and the prosthesis, as emphasized by Colonel Cutler, is rapid immediate movement of the prosthesis, even over small ranges.

DR. C. S. O'BRIEN, Iowa City: This operation is still on trial. We have had no trouble with corneal sensitivity. We lost several implants because in the first operation we excised the cornea and sutured the sclera around the peg. In the next operations the incision was grooved, and even then it pulled loose; but with the present meridional incision we believe that we have found the correct technic, although the one advocated by Dr. Hughes may be the answer.

### **Tenotomy of the Superior Oblique Muscle for Hypertropia.**

DR. RAYNOLD N. BERKE, Hackensack, N. J.

This paper was published in a previous issue of the ARCHIVES (38: 605 [Nov.] 1947).

#### DISCUSSION

DR. FREDERICK C. CORDES, San Francisco: Overaction of the superior oblique muscle is rare in our experience. When it does occur, it is the result of one of a number of conditions: (1) paresis of the inferior rectus muscle of the opposite side, (2) paresis of the homolateral inferior oblique muscle or (3) primary overaction of the superior oblique muscle. The last is probably rare, as the inferior oblique, being inserted higher and being a stronger muscle, has anatomic advantages.

The commonest cause of overaction of the superior oblique muscle is paresis of the contralateral inferior rectus muscle, and the treatment usually advocated is weakening the yoke muscle if the paretic eye is used for fixation. If the nonparetic eye is used for fixation, the paretic muscle should be strengthened and the antagonist weakened if spasm has developed. Most ophthalmologists are in accord with Sanford Gifford's statement that it is "inadvisable to disturb the opposite superior oblique."

Dr. Berke's operation seems safe, simple and logical, but one wonders whether the percentage of cases of complete loss of function will be so high that the operation will have to swing over to recession of the muscle at its insertion, as had to be done in the case of the medial and rectus inferior oblique muscles.

The importance of a correct diagnosis cannot be stressed too much. Overaction of the superior oblique is the description of a condition, and the diagnosis of the cause is of great importance in making the decision as to the procedure indicated. High lateral deviation had better be corrected before operation on the vertical muscles is attempted. In high degrees of deviation some of the vertical muscles are in the field of least action. For example, in high exotropia, owing to the oblique muscles being in the field of least action, one may obtain a faulty conception of their action unless these muscles are studied after the lateral deviation has been corrected.

My experience with the operation is limited to 1 case, and I had no difficulty in carrying out Dr. Berke's technic. The importance of not freeing the fine lateral fibrillae that pass from the tendon to the sheath bears emphasis.

DR. WENDELL L. HUGHES, Hempstead, N. Y.: Operations on the superior oblique muscle have been avoided by ophthalmologists for two reasons: difficulty of technic and difficulty of diagnosis. Abnormal action of the depressors of the eye are often difficult to determine.

Wheeler described an operation for increasing the action of the superior oblique by tucking the tendon, and in 1944 I presented the



operation of recession of the trochlea for reducing the action of the superior oblique (*Am. J. Ophth.* 27:1123 [Oct.] 1944). However, Dr. Berke's operation is superior, for several reasons:

It affords (1) greater ease of technic and (2) greater certainty of results, because of better exposure, and (3) the amount of weakening effect can be at least partially controlled.

I have performed the operation twice in the past month; in 1 case too much effect was obtained, and in the other a satisfactory result was obtained. If the tendon is severed too near the trochlea, the cut end may be retracted to or through the trochlea.

A comparison may be made with tenectomy of the inferior oblique muscle. In myectomy of the inferior oblique, if the capsule is removed with the piece of muscle, one may readily obtain complete paralysis; but if the muscle is carefully dissected from its capsule and only the muscle fiber is removed, one will not get complete paralysis. The muscle remains attached to its original position by means of the capsule.

I am of the opinion that the operation described is indicated in all cases in which there is any overaction of the superior oblique muscle, with or without reduced action of the associated inferior rectus of the opposite eye.

DR. RAYNOLD N. BERKE, Hackensack, N. J.: The first patient operated on eight years ago shows no signs of paralysis of the superior oblique. Overaction of the superior oblique is due, as Dr. Cordes stated, to weakness of the contralateral inferior rectus or to weakness of the homolateral inferior oblique; but, as Dr. Hughes pointed out, sometimes it is impossible to state which of these muscles is primarily at fault. Fortunately, in such cases tenotomy of the superior oblique is just as effective as in cases in which one is able to make a positive diagnosis. Over one-half our patients had an exotropia which was greater in the lower fields. This was attributed to the divergent power of the superior oblique muscles. The last patient whose case I presented had a hypertropia with an exotropia before operation. In this case both the lateral and the vertical deviation were corrected by bilateral tenotomy of the superior oblique muscle.

#### **Combined Red Filter and Occluder with Several Uses.** DR. WENDELL L. HUGHES, Hempstead, N. Y.

The author described an instrument consisting of a ground plastic red filter, blackened on one end with a handle in the middle and used with a green light at 20 feet (6 meters) for fixation. A quick method of determining the balance of the extraocular muscles, using the instrument and the proper prisms in the parallax test, was described. The instrument may be employed also as an occluder as well as for performing the alternate cover test and for checking gross fusion.

#### **Instrument for Use in the Recession Operation for Squint.** DR. ANGUS L. MACLEAN, Baltimore.

To avoid vertical heterophoria after a recession, an instrument was devised to facilitate the placing of the end of the recessed muscle in correct alinement with the original insertion.

## NECROSIS OF INTRAOCULAR TISSUES

BERNARD SAMUELS, M.D.  
NEW YORK

**I**N TEXTBOOKS on general pathology, considerable space is devoted to the study of the death of tissues. However, in the teaching of the special pathology of the eye, disease from this standpoint fails to receive the attention that its frequency and extent warrant.

In accordance with the nomenclature of general pathology, the term necrosis means the local death of cells or of tissues in an organ, notwithstanding the loss of which the organ as a whole continues to live.

Intimately associated with necrosis are the conditions of degeneration, atrophy and gangrene. Degeneration signifies an alteration in the metabolism of the cells that compose a tissue, but not to such an extent as actually to cause the death of the cells. Atrophy means acquired diminution in the size of cells or of tissues after maturity has been attained. Degenerated or atrophic tissue may be converted into necrotic tissue. Gangrene signifies necrosis but only that following an invasion of saprophytic organisms.

In ocular pathology the term necrosis is employed in a narrow sense, referring, unless otherwise qualified, to the death of the cells of a tissue, it being understood that the framework is spared and is capable of being resuscitated by the ingrowth of cells from the adjacent living tissue. For example, a piece of cornea, excised for the purpose of transplantation, may lose its corpuscles and remain in a state of necrosis until corpuscles in the receiving cornea have had time to divide and migrate into the graft.

Bearing in mind that knowledge is progressive, the present observations, based on a study of over 800 globes that showed necrotic tissue under the microscope, may be considered as a continuation, on a wider scale, of observations on intraocular necroses in two papers published in 1929<sup>1</sup> and 1933.

There are two types of intraocular necrosis, namely, the noninflammatory and the inflammatory type.

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From the Eno Laboratory of the New York Eye and Ear Infirmary.

Delivered as the deSchweinitz Lecture before the Section of Ophthalmology of the College of Physicians of Philadelphia, Nov. 20, 1947.

1. Samuels, B.: Necrosis of the Iris, *Tr. Ophth. Soc. U. Kingdom* **49**:421-436, 1929; A Study of the Anatomic and Clinical Manifestations of Necrosis in Eighty-Four Cases of Choroidal Sarcomas, *ibid.* **53**:520-570, 1933.

## NONINFLAMMATORY TYPE

## NECROSIS CAUSED BY CIRCULATORY DISTURBANCE

*Iridodialysis.*—The purest form of intraocular necrosis is that which is produced when the arteries, veins and nerves of the iris are suddenly and completely severed from their connection with the ciliary body. Usually the dialysis takes place in no more than a sector of the iris and then the actual necrosis is confined to the ciliary zone. The corresponding pupillary sector remains intact because its nutrition is maintained from the collateral circulation by way of the lesser arterial circle of the iris. Iridodialysis is commonly the result of injury, accidental or surgical; but it may be caused, very slowly it is true, by the extension of a malignant melanoma of the ciliary body into the anterior chamber, or,

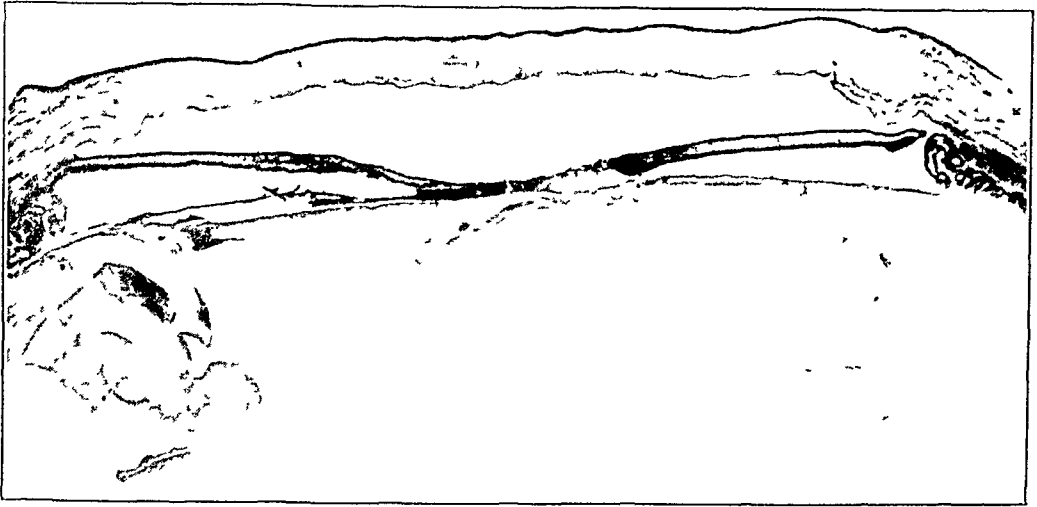


Fig. 1.—Slow necrosis of the iris on the right side due to dialysis; atrophy on the left side resulting from peripheral anterior synechia. The homogeneous and slightly edematous stroma, with a pocket of pigment granules at either end, characterized the necrosis

rarest of all, it may be spontaneous. The sector is thrown into shallow folds and the pupillary border is drawn in by the contraction of the sphincter muscle. The nuclear elements disappear from the stroma, seemingly one at a time. A few pale strands in a rarified matrix are all that is left of the walls of the blood vessels. For a long time no perceptible change takes place in the pigment epithelium, and then it only becomes thinner, as does the whole iris (fig. 1).

*Cyclodialysis.*—What happens to the ciliary muscle when the anterior ciliary arteries are severed was shown in 2 globes in which cyclodialysis occurred on one side. The corresponding part of the muscle was necrotic, whereas on the other side it was normal. In contrast to the necrotic part of the muscle, the ciliary processes and the iris were everywhere normal.

In 1 globe the long posterior ciliary artery and nerve had been severed on one side by a perforating wound back of the ora serrata. The iris and the ciliary processes on this side were totally necrotic, whereas elsewhere they were not affected and everywhere the ciliary muscle was normal. A similar necrosis would be produced by coagulation during diathermy should the artery and nerve be brought into the field of the puncture.

*Glaucoma.*—By far the greatest number of eyes studied showed evidences of glaucoma, since the conditions in which glaucoma plays a role are manifold. In glaucoma, no structure of the eyeball escapes damage, but the iris and the ciliary processes are the only ones that may be actually necrosed. In chronic simple glaucoma, atrophy of the iris is induced by the gradual arrest of the blood supply. In acute fulminating glaucoma, circulatory necrosis of the iris is induced by the sudden cutting off of the circulation. The length of time that any tissue is able to survive after the complete arrest of its blood supply varies, some tissues having greater power of survival than others. It is certain that the survival period of the delicate stroma of the iris is relatively brief, since partial or complete necrosis may follow the shortest attack of fulminating glaucoma. The pupillary zone of the iris is the part that is apt to be the most severely damaged, probably because the circulation is not so active as in the zone nearer the greater arterial circle. Hemorrhages are seldom seen with glaucomatous necrosis of the iris because the afferent and efferent vessels are blocked at the same moment (fig. 2).

In glaucoma the necrosis of the ciliary processes often coincides with that of the iris. It may be confined to the low cells of the apexes, or it may include some of the stroma. Necrosis of the ciliary processes may account for the sudden reduction of tension following a severe acute attack of glaucoma. The tension may remain low, probably because the processes are necrotic and cannot secrete the normal amount of aqueous.

Finally, in acute glaucoma not all the cornea is affected in the same way. Absence of corpuscles in the posterior central third, where the lymph flow must be more sluggish than at the base, is usual.

## INFLAMMATORY TYPE

### NECROSIS CAUSED BY PYOGENIC BACTERIA

Inseparably connected with necroses of intraocular tissues are deleterious, diffusible substances, generally and vaguely called toxins. No agent is more destructive to the inner layers of the eye than the toxins derived from pyogenic bacteria. Within the tissues themselves, after they have been rendered dead by circulatory disturbance or by

bacteria, secondary toxins develop which are capable of damaging the surviving parts to an extreme degree.

*Bacteria Ectogenously Located (in the Cornea).*—The cornea, because of its avascularity and accessibility, is the most favorable site in the entire body for the local effects of bacterial toxins. Axenfeld and Uhthoff, in 1896, discovered that the pneumococcus is the cause of the typical *ulcus serpens* of the cornea. The layers of the inner portion of the eye are proverbially sensitive, as is shown by the irritation following the irrigation of the anterior chamber with a solution too cold or, worse still, too warm, or with one the ingredients of which are not in exactly



Fig. 2.—Malignant melanoma of the choroid. The necrosis of the iris and of the posterior middle layers of the cornea is due to the pressing forward of the lens, and not directly to the tumor. Blood vessels in the iris appear as streaks parallel to the surface in a homogeneous matrix.

the right proportions. The toxins from a *serpiginous ulcer* diffuse into the aqueous, probably in extraordinarily small quantities. Nevertheless, they are able to set up a condition of intoxication, pure and simple, and profound enough to cause necrosis of the iris and hyperemia of the blood vessels of the ciliary processes and, to a less extent, those of the retina. The necrotic iris may be so swollen and edematous as to attain twice its normal thickness. Because of the loss of its nuclear elements, the stroma takes on a characteristic ghostlike appearance, in the midst of which hyalinized walls of vessels filled with blood are often seen. Owing to the diluting effect of the flowing blood, the endothelial lining of the vessels is preserved. The sphincter muscle, being resistant, may be

present on one side and absent on the other. The pupillary zone is the part most affected, just as it was noted to be in necrosis from circulatory disturbance. Then, too, the pupillary zone is thin, and it is through its sharply pointed opening that toxins must pass on their way to the posterior chamber.

When toxins come from the cornea, the stroma of the iris affords a certain amount of protection to the pigment epithelium lining its posterior surface except at the pupillary margin, where the two rows of pigmented cells bend forward over the sphincter muscle. These particular cells react by swelling, bursting and setting free their pigment granules. This they do, albeit far more slowly, in cases of low grade uveitis and in extreme old age. The first effect of the toxins as they attack the pigmented cells on the posterior surface of the iris is to dissolve the cement substance that binds the cells together, whereupon the cells, free from tension, lose their tall pyramidal shape and become round. As a still more striking pathologic feat, they take on the power of locomotion, often wandering forward into the iris, singly or in groups, as though to find refuge from danger. In this way, in necrosis of the iris in its recent state three orders of round pigmented cells are to be differentiated in the stroma (fig. 3). The normal clump cells are recognized by their intimate relation to the sphincter muscle. The chromatophores draw in their processes and become rod shaped or round. They are the least pigmented of all. The intensely black cells are those from the pigment epithelium, and these may make their way forward into the anterior chamber.

From an anatomic point of view, the ciliary processes are particularly susceptible to toxins. They are thin, and the two epithelial layers that cover their apices are composed of low cells; moreover, the pigmented row is lightly pigmented. In the most virulent cases of corneal ulcer, the ciliary processes may become necrotic concomitantly with the iris.

The reaction of the iris to the toxins arranges itself in two stages, a fact which explains the long-lasting irritability of the eye after the corneal lesion has healed. In the first stage the reaction is directed against the primary toxins from the pyogenic bacteria. It is marked, as stated, by necrosis of the stroma and by the formation of a hypopyon, many of the cells of which have migrated from the ciliary processes. The character of a hypopyon varies. It contains mostly pus cells, with more or less fibrin, to which are added desquamated endothelial cells and occasionally blood. The reaction is cumulative, increasing in intensity as long as the bacteria live. In the second stage, which sets in as soon as the bacteria die, the reaction is directed against the secondary toxins which emanate from the dead portion of the iris and from the necrotic hypopyon. Myriads of fresh polymorphonuclear leukocytes migrate

from the parts that have been saved into the necrotic iris and hypopyon to start the process of organization. The general surgeon recognizes the toxic action of dead pus and takes precautions against its accumu-



Fig. 3.—Traumatic necrosis of the iris in the earliest stage. The pupillary zone is edematous and appears ghostlike. The pigmented cells are of three orders—clump cells, chromatophores and cells from the pigment layer.

lation by means of posture and irrigation. Acting on the same principle, the ophthalmic surgeon in treating a corneal ulcer, when the hypopyon is excessive, opens the chamber and removes the hypopyon in order to shorten the reaction.

That a necrotic iris is in itself noxious was proved in a study of several globes of the series in which the epithelium of the lens was killed in a stretch corresponding exactly to that occupied by the overlying adherent necrotic iris, whereas, in contrast, in the exposed pupillary area the epithelium remained normal. The organization of a necrotic iris takes place with great rapidity, and the contraction may be so extensive that the structure may be reduced to a dense vascular stump in the angle. The disappearance of a sector of the iris into the angle within a few days after a cataract extraction with round pupil is too rapid for atrophy—most likely it is necrosis (fig. 4). In the edematous phase a necrotic elevated sector of the iris would be too pulpy to be seized with

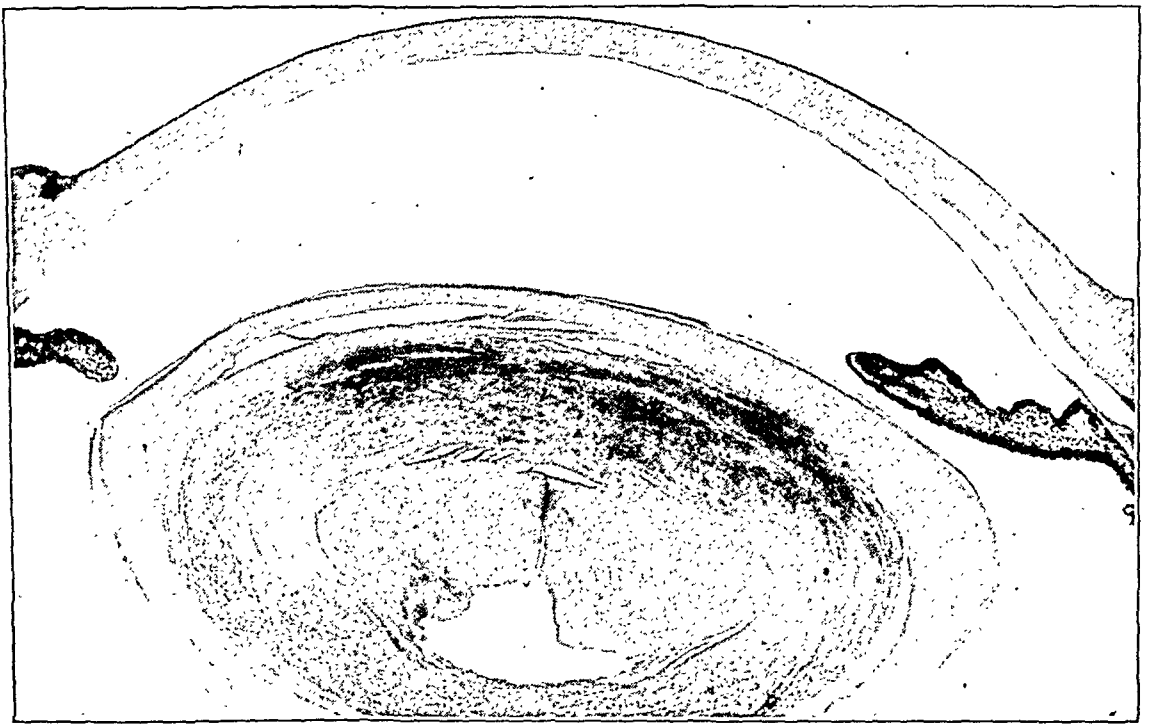


Fig. 4.—To the left, a very cellular and vascular stroma, after necrosis with organization, bears no resemblance to the original structure.

the forceps, whereas an atrophic sector could be picked up—and it is surprising how much resistance an atrophic iris may offer to traction.

*Bacteria Endogenously Located.*—(a) In the Anterior Chamber: When the bacteria are lodged within the anterior chamber, an infection is set up, in contradistinction to an intoxication, when the bacteria work from the cornea. Attacking the cornea from the chamber side, the bacteria first produce the disappearance of the endothelium on Descemet's membrane and of the corpuscles between the lamellas of the posterior third of the cornea.

The infection in the anterior chamber may attain such force that it not only kills the corpuscles but coagulates the lamellas, causing them to



fuse in one swollen opaque, homogeneous layer. Generally the most anterior lamellas, together with Bowman's membrane and the epithelial covering, escape, no doubt owing to the greater distance from the origin of the toxins and to the diluting effect of the flowing conjunctival secretion.

Every totally necrotic area, no matter where it is, may be considered an irritating foreign body. Hence the reaction to a dead cornea is of

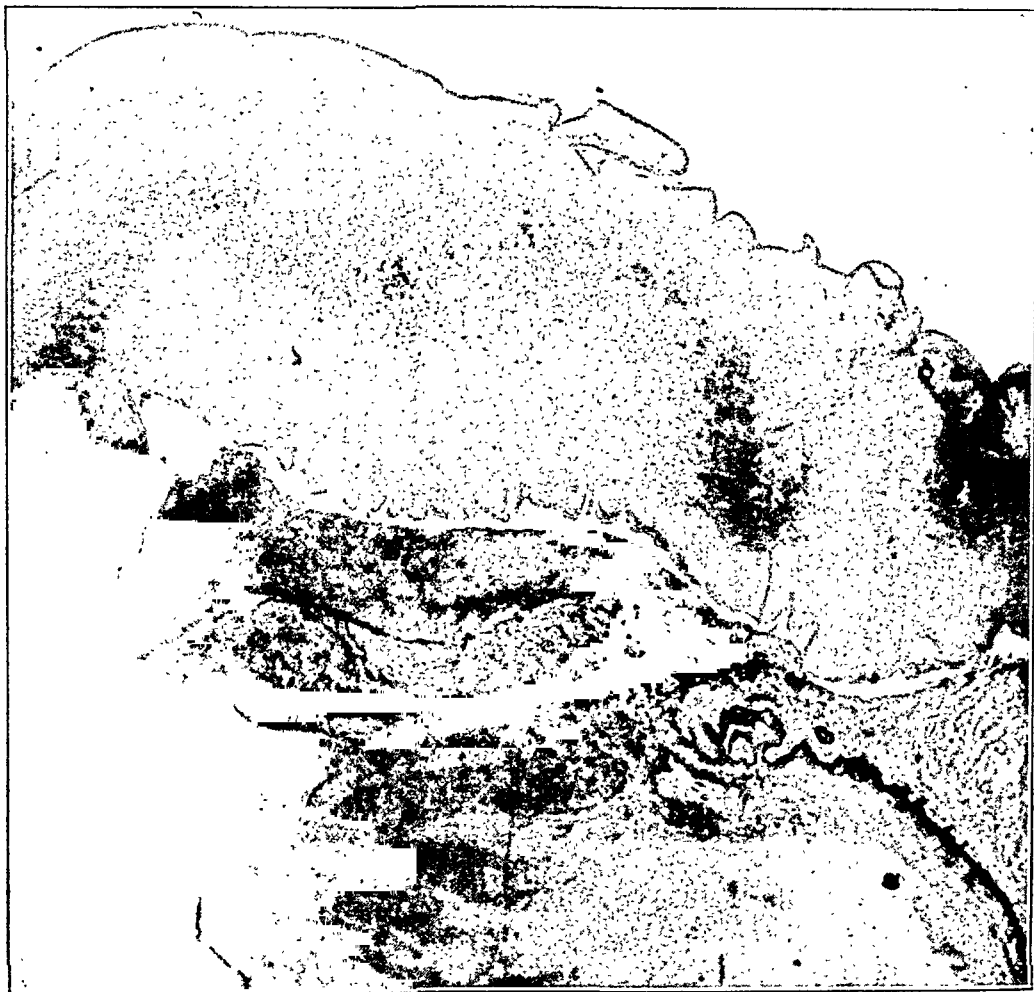


Fig. 5.—The cornea is swollen to twice its normal thickness. In the posterior layers both nuclei and lamellas are dead, as a result of toxins from the anterior chamber. To the right there is a collection of pus cells (ring abscess). The iris is necrotic, but the pigment epithelium, being protected by the stroma, is remarkably well preserved.

the nature of a demarcating process, distinguished by the migration of countless leukocytes into the periphery of the cornea, forming a swollen, yellowish wreath; whence comes the name "ring abscess" (fig. 5). The leukocytes are prevented from entering the slough by the negative chemotactic action of the secondary toxins therein generated. However, they

aid in the liquefaction of the partially necrotic lamellas that bind the dead to the living tissue, so that the former may be expelled. It is said that leukocytes will attack tissue only after it has been damaged and that there is no evidence that they will attack normal tissue, a fact which explains the return to normal of a broad, swollen, yellowish gray zone that surrounds a corneal ulcer.

In all cases of toxins in the aqueous the condition of the angle of the anterior chamber is to be taken into account. When the angle is open, the outflowing aqueous takes care of toxins for a certain time. When the angle is blocked, the concentration of the toxins starts from the beginning.

(b) In the Vitreous Body: 1. Endophthalmitis septica. When an infection is confined to the anterior chamber, there is hope for the retention of the eye. When the bacteria are located in the posterior chamber or in the vitreous body, the prognosis is invariably bad because of the involvement of the ciliary body. In the earliest days of bacteriology it was thought that the virulence of pyogenic bacteria was due to the disturbance in the vital processes of their host by the mere mechanical effect of their presence. The extreme minuteness of pyogenic cocci may be inferred from the fact that eight to ten may be strewn across one red blood cell. In the laboratory, colonies of bacteria are seldom found in the slides of eyes that have been removed because of infection. The bacteria that induce the ordinary intraocular infection seem to be short lived. It used to be taught that bacteria kill a tissue by robbing it of substances necessary to its metabolism. It is true that bacteria do derive their food from their host, but it is by means of the toxins into which this food is converted that the harm is done.

Bacteria lodged within the vitreous body, as elsewhere, require a certain period for multiplication and evolution before they can create toxins. The latter irritate the ciliary body and retina and call forth the migration of pus cells toward the bacteria in the vitreous, where they localize to form an abscess. This inflammatory process is known as endophthalmitis septica. This is the mildest form of infection of the vitreous, so mild that the delicate, highly organized retina is not destroyed. The leukocytes come mostly from the very vascular ciliary processes and in less amount from the less vascular retina. The abscess soon becomes necrotic and of itself irritating, as occurs with a hypopyon. The first steps in the organization of the dead mass come from the ciliary body, on which account the detachment of the retina begins anteriorly. The detachment is the principal cause of the loss of vision. The essential feature in endophthalmitis septica (abscess of the vitreous) is the preservation of the inner layers of the eye, the loss of cells being no greater than in an ordinary inflammatory process.

2. Panophthalmitis septica. This condition is characterized by total and widespread tissue death. No part of the eye escapes. When the primary seat of the infection is in the vitreous, the first layer to be destroyed is the retina, opening the way for the bacteria to attack and destroy the choroid by suppuration. The infection spreads through the sclera into the space of Tenon, setting up an orbital cellulitis, with its clinical entity of chemosis of the conjunctiva, exophthalmos and immobility of the eye. The essential feature of panophthalmitis septica is what may be termed universal tissue death.

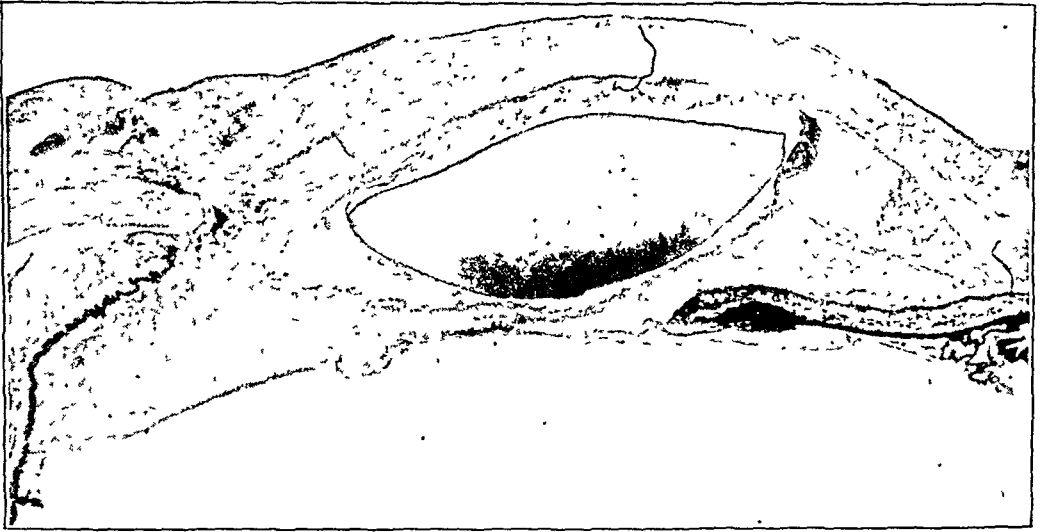


Fig. 6.—To the left, tags of iris are seen in the wound. The cornea here is replaced by thin, wavy bundles of connective tissue. The central lamellae are devoid of nuclei, and the iris is necrotic. A pocket of necrotic cells of the pigment layer lies in the pupillary zone. The sharply defined nucleus, surrounded by a phagocytic zone, is somewhat displaced by artefact.

#### NECROSIS CAUSED BY THE RETENTION OF LENS MATTER

The necrotizing effect on the iris and cornea of a large amount of lens matter, particularly the nucleus, retained in the anterior chamber, is strikingly like that caused by colonies of bacteria in the same location. The onset of reaction to the toxins emanating from the necrotic material is more retarded but it is cumulative until the material has been absorbed or entirely encapsulated. The increasing intensity of the reaction may be judged from the study of the case of a man aged 74 on whose eye, six weeks before enucleation, an attempt had been made to extract the lens. Clinically, the cornea was swollen and completely opaque. There was excessive chemosis of the conjunctiva, accompanied with excruciating pain. A diagnosis of panophthalmitis septica was made. Microscopically (fig. 6), a hard nucleus, entirely surrounded by a zone of phagocytes,

lay against the cornea. It had produced complete destruction of the cornea, so far as it touched it, and the replacement of the normal lamellas with ordinary wavy connective tissue. The presence of light perception and the absence of exophthalmos should have spoken against the diagnosis of panophthalmitis. A small, circumscribed, grayish defect in the stroma of the iris sometimes marks the site once occupied by a portion of lens substance that had been slowly absorbed. Small areas of necrosis cause little reaction.

#### NECROSIS CAUSED BY TRAUMA

Immediate and final tissue death is exemplified by the damage inflicted on the cornea by heat arising from splashes of hot metal or by chemical reaction produced by strong acids. Inflammatory toxic reactive processes come into play, the object of which is to get rid of the dead irritating tissue and to repair the part. The general principles involved in eliminating the dead material are exactly the same as those operative if death had been caused by circulatory disturbance or by the action of bacteria, instead of by direct injury.

In cases of corneal scars from caustics, it is not easy to estimate the damage that has been done to the inner structures at the moment of the accident, or afterward, by the absorption of toxins from the sloughing surface. In a case of lime burn in the present series that had long been quiescent, light perception and projection were prompt; an attempt, therefore, was made to improve vision by stripping off a membrane that was believed to lie lightly over the cornea. Owing to postoperative inflammation, the eye was enucleated. The cornea in almost its entire thickness was replaced with scar tissue, and the anterior chamber was partly occupied by an organized exudate. The iris was necrosed. The entire field was sealed off by a cataractous lens and a cyclitic membrane, leaving the posterior part of the eye normal and accounting for the retention of some sight.

Since the cornea is thick and resistant and the eye is supported by a cushion of fat in the orbit, it is seldom ruptured by a blow. The cornea may, however, be severely crushed by the direct action of a blow. In a case of this kind in the series, in which the injury was due to contusion, both corpuscles and lamellas in the middle layers of the cornea had been completely destroyed. The clinical effect was that of disciform keratitis from infection. After an inflammatory reaction of long duration, the dead mass in the cornea was liquefied and absorbed, being replaced by thin, wavy bundles of ordinary connective tissue, traversed by deep blood vessels. A cellular membrane lined the chamber side of the cornea. The iris was partially necrotic and densely infiltrated, apparently as a result of intoxication from the cornea, rather than of injury.

The reactions offered by different tissues to blows were shown in a case in which a sector of the iris had been dialyzed by a blow and yet there was no change in the cornea. Another case was informative as showing that the irregular white spots seen in the fundus after a severe contusion of the globe may not be the naked sclera. In this instance a thin band of avascular connective tissue lay over the sclera, replacing the area in the choroid and retina which had been necrosed by the contusion. Organization of a necrotic matrix proceeds rapidly in the choroid because this coat is very vascular and is protected on one side by the sclera. In a case of complete rupture of the choroid it is probably the naked sclera that is seen clinically.

In the study of the cases of prolapse of the uvea it was brought out that whenever the prolapse is covered with conjunctiva, no matter how constricted is the neck or how long the prolapse has existed, it is seldom necrosed. However, when the prolapse lies uncovered in the cornea, it quickly dies. Sloughed material is an excellent pabulum for bacteria. In my experience, prolapsed uvea in the cornea is particularly dangerous for the development of sympathetic ophthalmia.

#### NEUROPATHIC NECROSIS

To cite a familiar example, neurokeratitis paralytica, it was believed that section of the trigeminus nerve or excision of the gasserian ganglion leads to necrosis of the epithelium of the cornea. It is now known that there is no actual death of the epithelial cells but that the loss of control over their metabolism exercised by the sensory fibers of the trigeminus nerve merely reduces their vitality and renders them less able to withstand mechanical injury or changing atmospheric conditions. The cornea maintains itself as long as it is protected by closure of the lids.

*Acute Neuropathic Necrosis of the Uvea.*—1. Herpes of the Iris: It is established that herpes zoster is a specific, self-limited, unilateral inflammatory disease, caused by a filtrable virus. In herpes zoster ophthalmicus the usual primary site of the lesion is said to be in the gasserian ganglion. A few cases of herpetic iritis have been reported in which a heavy inflammatory infiltration was observed in the sheaths of the posterior ciliary nerves near the optic nerve. These nerves lose their sheaths in the emissaria, so that almost naked, flattened nerve fibers descend in the perichoroidal space. It is, therefore, surmised that at all events the virus passes toward the periphery along the nerve fibers. But it is another question as to the way in which the diseased nerve fibers produce tissue death. One theory is that chemical changes, having destructive powers, take place in the nerve endings. It is certain that mere section of the trigeminus nerve does not produce an inflammatory reaction in the uvea, in the absence of inflammation in the nerve itself.

Herpes of the iris is characterized by eruptive, circumscribed, reddish elevations on the surface of the iris, similar to those on the skin, and in very severe cases accompanied with hyphema. When the iritic eruptions are concurrent with those on the skin and cornea, there is never a question as to the diagnosis. But herpetic iritis may occur alone, without any scars on the skin or cornea. The pathologic picture, in fresh eruptions, is more typical than the clinical. It is distinguished by the excessive amount of necrosis in the stroma of the iris, identical with the inflammatory toxic type of necrosis produced by pyogenic bacteria. The reaction takes the form of a heavy plastic iridocyclitis, often with precipitates on the cornea. In the end each eruptive focus is replaced by connective tissue. Doubtless, there are cases of herpetic iritis which are not clinically typical, just as there are cases of herpetic keratitis in which the diagnosis can be made only by the concurrent typical lesions in the skin. Many eyes are enucleated because of a diagnosis of intractable iridocyclitis which came on suddenly, was unilateral and for which no cause could be found. In some of these cases the iritis is possibly of neuropathic origin, although the anatomic examination may throw little light on the cause, because secondary changes soon obscure the primary necrosis produced by the virus.

2. *Acute Primary Necrosis of the Uvea:* Cases have been reported in which the necrosis of the iris and ciliary body has come to anatomic examination in the fresh state, uncomplicated as yet by any signs of reaction. As in these cases bacteria, glaucoma and trauma, in short, all the conditions that are known to produce necrosis, are excluded, clinically and pathologically, the condition has come to be known as acute primary necrosis of the uvea (fig. 7).

#### NECROSIS OF MALIGNANT MELANOMA OF THE CHOROID CAUSING NECROSES OF PREEXISTING TISSUES

It is difficult to be original in discussing any phase of the life of intraocular tumors, for this subject was covered in detail by the elder Fuchs, on whose exact studies, chiefly cellular, the pathology of the eye has largely been developed. There is nothing singular in the spontaneous death of an intraocular malignant melanoma, since such is the common fate of all neoplasms. However, to the oculist the death of a malignant melanoma of the choroid is of prime importance, for toxins from this source may set up an extremely flagrant iridocyclitis, combined with the highest tension, creating a picture difficult to distinguish from that of the ordinary acute fulminating glaucoma. The toxins derived from necrosis of a malignant melanoma, although of tissue origin, may be fully as destructive as those elaborated by virulent pyogenic bacteria, as in panophthalmitis. It is singular that the toxins from a melanoma seem

to be more destructive than those from a retinoblastoma, which is largely necrotic from the start. A melanoma may grow to fill the vitreous cavity and yet cause neither increase of tension nor inflammatory reaction. It grows slowly, replacing structures by pressure atrophy. Its presence is not the direct cause of glaucoma. This is brought about by pressure of the subretinal fluid, which, being greater than that of the vitreous, pushes the lens forward. The largest tumor causes no inflammatory reaction so long as it is not necrotic. A necrotic mass in a tumor means totally dead material, including fibrous and cellular elements.

*Necrosis of the Tumor.*—1. Relation to Its Size and Shape and the Type of Cells: As with other tumors, the larger the melanoma the more apt it is to become necrotic; nevertheless, this may happen when it is

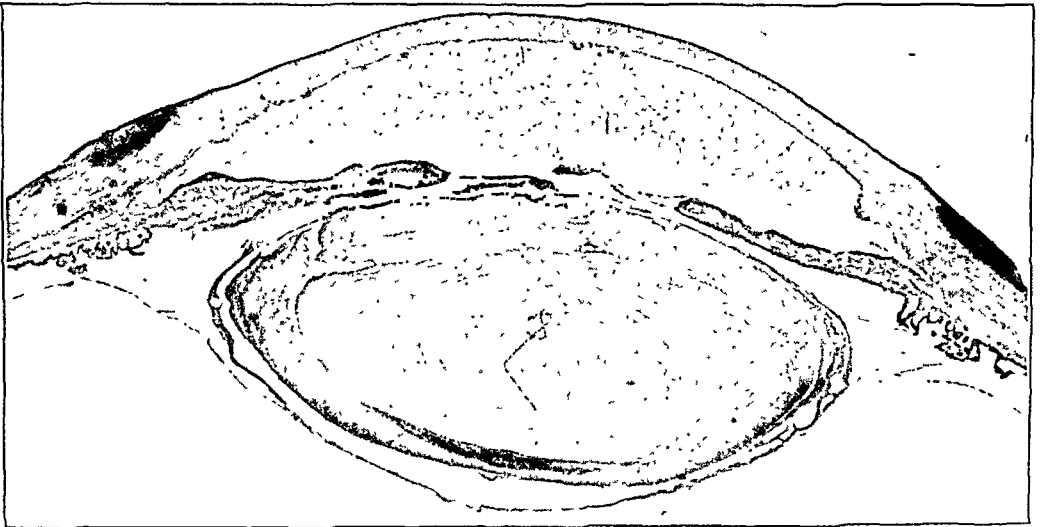


Fig. 7.—Unilateral plastic iritis with deposits on Descemet's membrane. The iris is in the inflammatory stage of necrosis. Note the loss of substance in the central area to the left and the dispersion of the pigment epithelium. As no clinical or pathologic cause could be found, the condition was called acute primary necrosis of the iris.

no larger than a cherry seed. The blood vessels of the tumor are continuous with those in the host. The cells farthest from the blood vessels, which are generally mere endothelial tubes, are the first to perish. It is not understood why a tumor which hitherto has shown no signs of tissue death suddenly becomes necrotic throughout. Most tumors are composed of different types of cells, spindle cells being in one part, round cells in another. In the matter of necrosis, the type of cell seems to make little difference. A mushroom-shaped tumor is more apt to necrose than a flat, infiltrating one, and the head of the tumor is the most often affected, as is the case with any pedunculated growth.

2. Location of the Dead Mass Within the Tumor: Groups of dead cells are encountered in almost every melanoma. They produce no

reaction; neither do larger areas, provided they are nowhere near the surface. In some tumors bands of connective tissue surround necrotic areas, indicating that a process of decay and repair has gone on at intervals. Most melanomas are located in the posterior half of the choroid; but it is chiefly on the structures in the anterior half of the eye that their necrotic action is directed.



Fig. 8.—A necrotic base of a malignant melanoma has partially destroyed the sclera and produced an inflammatory membrane, replacing the space of Tenon.

*Necrosis of Preexisting Tissues.*—1. Necrosis of the Sclera: In a case of mushroom-shaped melanoma the necrosis took place at the base of the tumor, directly in touch with the sclera (fig. 8). So concentrated were the toxins that the sclera was replaced by pus, which discharged itself into the space of Tenon. The type of pus from tissue necrosis is referred to as “unnatural” pus, in contradistinction to “natural” pus



from bacteria. In a case of this kind there is no immediate danger of the tumor finding its way out by the defect in the sclera, because the death of that part of the tumor antedates the defect and is the cause of it. If a fresh growth of cells should ever reach the defect, it would have to break through a thick cicatricial membrane before it could invade the orbit.

2. Necrosis of the Choroid: Although a melanoma originates within the choroid, the normal part of the choroid is the least likely of all the layers of the eye to undergo necrosis. Necrosis at the base of a melanoma is prevented from extending into the adjacent choroid because of its rich blood supply. When the retina is completely detached, toxins from a necrotic area in the inner layers of the tumor, in order to reach the choroid, must pass through the subretinal fluid and, in doing so, be diluted. On its inner surface the choroid is protected from irritating substances by the pigment epithelium, the lamina basalis (vitrea) and the choriocapillaris, and on its outer surface it is protected by the sclera. In response to extremely virulent toxins, the cells of the pigment epithelium fall away from one another, as in the iris, become round and, in order to find room, mount in groups over the lamina basalis. Sometimes a row of dead cells is detached from the smooth surface of the lamina as a result of serum derived from the choroid. A membrane or the retina adhering to the tumor serves to hold toxins back. In 1 case a membrane over a necrotic area on the anterior surface of the head of a mushroom-shaped tumor saved the overlying ciliary body and iris, while, at the same time, the opposite structures showed necrosis.

3. Necrosis of the Retina: Death is the only way by which the highly organized retina can react to virulent toxins. It literally falls to pieces. In lowly connective tissue the nuclei are the first to disappear, but in the highly organized retina the frail supporting fibers go first. The nuclei, although dead, can be identified for some time floating about in the fluid vitreous. A particularly vulnerable part of the retina, in all circumstances, is at the ora serrata, where it is faded away, leaving the rest of the retina to fall back on its inner surface.

4. Necrosis of the Papilla: In some cases of the series the papilla was deeply excavated, but seldom to the extent seen in chronic simple glaucoma. A pathologic excavation and peripheral anterior synechia make it clear that glaucoma has antedated the necrosis. In the severest cases of tumor necrosis the papilla may be converted into an indefinite, weblike groundwork lying over the lamina cribrosa, beyond which an inflammatory reaction can be traced along the blood vessels. Pigment granules may be observed far back along the inner surface of the pial sheath. The granules have their origin in the bursting of cells of the

pigment epithelium of the choroid and are carried into the nerve in the bodies of phagocytes. They are not to be mistaken for tumor cells.

5. Necrosis of the Ciliary Body: Not all parts of the inner surface of the ciliary body are affected equally by toxins. The best preserved cells are in the deep recesses of the ciliary valleys, out of the way of the poisonous currents. Attacked by concentrated toxins, the nonpigmented layer disappears completely. Owing to the surface indentations into which the cells of the pigment layer dip, this layer is not detached as readily as is the corresponding layer on the smooth and even lamina basalis of the choroid. In very severe cases of tumor necrosis the stroma of the ciliary processes is destroyed, leaving loops of congested blood vessels projecting naked into the circumlental space. The circular bundles of the ciliary muscle are often partially missing, but the longitudinal bundles are seldom much affected. In only 1 instance in the entire series was the ciliary body totally destroyed, and the nuclei of the sclera were missing as far as its external surface.

6. Necrosis of the Iris: As with the ciliary body, it is the rule for the side of the iris next the tumor to be the more affected. It is convenient here to mention a point of clinical diagnostic value: The episcleral blood vessels over a tumor are likely to be dilated, in comparison with those of the other side. The thick pigment epithelium of the iris and the dilator muscle protect the stroma of the iris from toxins coming in this direction, in the same manner in which the stroma protects these layers when the toxins attack from in front.

The damage done to the preexisting tissues as a whole corresponds in general with the size of the necrotic tumor. In 1 case a large posterior tumor had suddenly become necrotic, and simultaneously the eye showed universal necrosis. The lens had fallen back so that the iris and cornea were attacked through an open route, in full force, and sudden death was meted out to both. In the iris some of the chromatophores had no time to gather in their processes, and they, with the columnar cells of the pigment epithelium, were struck dead in their normal place and shape. The endothelium of the cornea vanished, as did the corneal corpuscles, the lamellas taking on a homogeneous aspect, as in "ring abscess" (fig. 9).

7. Necrosis of the Vitreous and Zonule: In any extensive necrosis of the uveal tract there seldom remains more than a vestige of the vitreous and zonule. These structures, together with the cement substance between the cells of the pigment epithelium, seem to have no resistance.

8. Necroses of the Lens: Invariably, the lens capsule was distended. The interval between the onset of the necrosis and the removal of the eye is too short for the formation of an anterior polar cataract. Only one such cataract was found and this was of great interest because the tumor

showed healed foci of necrosis which had probably set up a quiet attack of iridocyclitis from time to time. The lens was dead in every sense (fig. 10).

#### REACTION AND HEALING

Dead tissues are in themselves not capable of response. The violent inflammation and intractable pain set in, not at the moment of the necrosis, but later, after the toxins have had time to diffuse through the sclera and arrive on its surface in a diluted form. It is the reaction in the episcleral and orbital tissues that manifests itself clinically. Within



Fig. 9.—Necrosis of a large malignant melanoma of the choroid. The posterior lamellae of the cornea are without nuclei. The free space is an artefact, and the dark area is blood. The iris is totally necrotic, and to the right it appears as a mere shadow. The zonular fibers are dissolved, and the lens has fallen back.

the eye, a fibrinous, plastic exudate is thrown out by those preexisting tissues that survive, mostly from the sclera, and in time all dead parts are replaced by dense connective tissue. An ordinary cyclitic membrane is delimited from the vascular layer of the ciliary body by the pigment epithelium. In necrosis the pigment epithelium is destroyed, so that the membrane, containing pigment granules, scattered freely or held in phagocytes, is matted with the remains of the ciliary body and iris. Rapid shrinkage of the eye ensues, far more rapid than ever occurs in ordinary iridocyclitis.

It is conceivable that every tumor cell is dead and that the shrunken globe represents a spontaneous regression of the disease. This may also happen in cases of retinoblastoma. With either neoplasm such an event must be extremely rare. Somewhere a few melanoma cells survive and multiply to fill the shrunken globe and to break out in time through the fibrous envelope and push the stump of a globe forward.

#### NECROSIS ARTIFICIALLY INDUCED

1. *As a Therapeutic Measure.*—It is interesting that two diseases of the eye, retinoblastoma and detachment of the retina, formerly considered

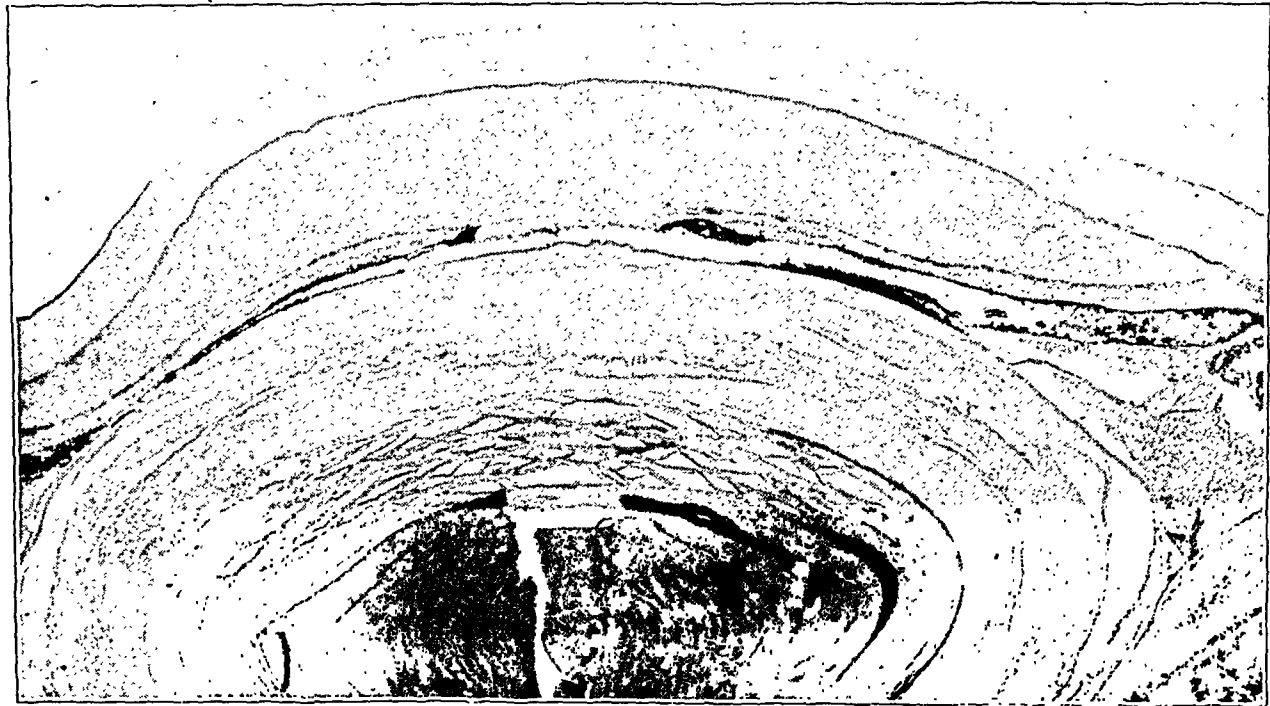


Fig. 10.—Necrosis of the iris superimposed on atrophy, caused by toxins from an almost completely necrotic malignant melanoma of the choroid. The corpuscles are absent in the posterior layers of the cornea. The pigment epithelium of the iris is detached on the right side. There is an anterior polar cataract.

hopeless, may now be cured by the induction of tissue death. It is one of the triumphs of irradiation that the rays can be so concentrated and directed as to destroy the neoplasm without damaging the normal structures of the eye. One theory is that the necrosis is brought about by the rays as the result of closure of the blood vessels, and not as the result of the direct action on the cells.

2. *As a Surgical Procedure.*—In diathermy for reattachment of the retina, each separate puncture through the sclera causes a break in continuity which has to be repaired. Bordering each hole in the sclera is a zone of total coagulation necrosis, cells and bundles of connective tissue all being killed. Surrounding this is another zone of incomplete coagula-

tion, in which the cells only are killed. The result is that from the two zones inflammatory toxins spread into the adjoining sclera and choroid and into the retina, once it is brought into opposition. Time must elapse before the inflammatory reaction can produce the cohesion of the retina, choroid and sclera. The greater the damage to the parts, the longer delayed and the severer the reaction. This may manifest itself clinically by the escape of red blood cells in the tissues or hemorrhage into the vitreous.

Each whitish spot that in time marks the site of a puncture represents much more than a similar-looking spot left after the healing of a focus of naturally produced chorioretinitis. The artificially produced spot is in reality the protrusion of a sheet of compact scar tissue that encompasses the sclera and is inseparably interwoven with it.

A wide expanse of the sclera is sometimes punctured in one or more operations, and often the coagulated areas infringe on one another, so that a large area of the fibrous tunic of the eyeball is made necrotic and must be replaced by tissue, baser than the original, which process requires an indefinitely long period. To gain more intense reaction within the eye, the surface of the sclera is cauterized until its bundles shrink and quiver. There is also the trauma involved in making a large exposure and in tenotomizing a muscle. In obliterating the perichoroidal lymph space, its lamellas and the nerves, arteries and muscle fibers that lie in the space are destroyed. The lymph space of Tenon is effaced. These artificially produced changes, summed up, must play a potent role in the causation of the uveitis and cataract that not infrequently develop a few months, or a few years, after diathermy, even when the retina is in place.

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## INCIDENCE OF DEFECTIVE COLOR VISION 'AMONG PSYCHOTIC PATIENTS

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INTEREST in the incidence of color blindness among psychotic patients has recently been aroused by the report in 1945 of Kaplan and Lynch<sup>1</sup> from the Hudson County Hospital of Mental Diseases, Secaucus, N. J. These authors concluded that psychotic patients, both male and female, show a high incidence of defective color vision. Of a group of 223 male schizophrenic patients, for example, they claimed to find evidence of defective color vision in 32.8 per cent, and of a group of 148 female schizophrenic patients, in 4.8 per cent. The generally accepted values for incidence of anomalies in color vision among male and female persons of the white race are, in round numbers, respectively, 8 and 0.5 per cent. The incidence claimed by Kaplan and Lynch is, then, approximately four times as great in male and nine to ten times as great in female psychotic subjects as that among subjects who are not mentally disoriented. The theoretic implications of this observation are of sufficient importance to warrant further investigation of the subject.

This is particularly evident since these results are at variance with the values reported in 1935 by Millard and Shakow<sup>2</sup> from the Worcester State Hospital, Worcester, Mass. These authors argued convincingly that it is necessary to use "stricter-than-the-usual criteria for diagnosing color-blindness" in a psychotic population, that evidence must be had that the responses given to the test for color blindness indicate a real defect in color vision, not merely agnosia-like symptoms, false perception or lack of concentration. Using such criteria, they concluded that the incidence of color blindness in a psychotic population,

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1. Kaplan, H. M., and Lynch, R. J.: Color Blindness in the Psychoses, *Am. J. Psychiat.* **101**:675-676 (March) 1945.

2. Millard, M. S., and Shakow, D.: A Note on Color-Blindness in Some Psychotic Groups, *J. Social Psychol.* **6**:252-256 (May) 1935.

such as the one studied by them, in which 839 cooperative subjects were examined, including 329 male and 301 female schizophrenic patients, is not significantly different from that in the normal population.

In evaluating these two studies, several questions are raised which lead to opposite conclusions. These refer to the tests used to detect the presence of defective color vision, the criteria used in diagnosis and the administrative procedure.

#### REPORT OF MILLARD AND SHAKOW<sup>2</sup>

Millard and Shakow employed the Ishihara test.<sup>3</sup> This test had been used extensively by Miles, Garth and others in studying normal populations, and it was fairly well understood in 1935 what type of response could be expected from persons whose color vision is normal and what type from those whose color vision is defective. Miles's criterion<sup>4</sup> for diagnosing color blindness was widely adopted. He omitted from the test the 3 plates designed for illiterate subjects (the "path" plates), as well as plates 10 and 11, on which a digit is supposedly read only by those with defective color vision but actually is seen by many whose color vision is normal. When, then, 11 of the original 16 plates of the Ishihara test are used, Miles's criterion for anomaly in color vision is 2 or more plates incorrectly read. It should be noted that this criterion was based on the responses of 1,286 male university students, of whom 8.2 per cent had color vision diagnosed as defective. The diagnosis was based on the Ishihara test alone, without supporting evidence from other tests. Moreover, the group examined comprised a highly selected sample of the population as to age and intelligence. A strict application of Miles's criterion to all subjects is not, therefore, *a priori* valid.

It is known that insignificant errors in reading the plates may be due to factors other than defective color vision—for example, low visual acuity, inattentive observation of the plates and, in a psychotic population, false perception or report. To meet this difficulty, Millard and Shakow divided the responses to the plates of the Ishihara test into four groups: correct, color blind, anomalous (in which the correct or the "color-blind" figure was seen in part, or the response was apparently due to some bias of the subject) and doubtful (in which the response was anomalous but definitely suggested that the subject saw a figure which is considered to indicate a color-blind response). They experimented with several criteria, the most logical and successful of

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3. A personal communication from Dr. Shakow indicates that the fifth edition of the Ishihara test was used.

4. Miles, W.: One Hundred Cases of Color-Blindness Detected with the Ishihara Test, *J. Gen. Psychol.* 2:535-543 (Oct.) 1929.

which they called the Worcester III criterion. According to this, two or more definitely color-blind responses, excluding those to plates 10 and 11, were required as evidence of color blindness. On this basis, no color-blind female patient was found among the 301 examined, all of whom were schizophrenic; 8 per cent of the male psychotic patients (538) and 8 per cent of the male schizophrenic patients (328) were found to have defective color vision. By the Miles criterion, which Millard and Shakow felt to be inapplicable to the type of subjects they were examining, these percentages were 13 for the male and 3 for the female schizophrenic group. Millard and Shakow stated that, in their opinion, the incidence of color blindness in Miles's population would not be materially changed by adoption of the Worcester III criterion and that it is valid to compare the percentage of color blindness found by Miles in a normal population with the percentage they found in a psychotic group.

#### REPORT OF KAPLAN AND LYNCH<sup>1</sup>

In this study, the American Optical Company's compilation of Pseudo-Isochromatic Plates was used. This test is a compilation of some Ishihara and some Stilling plates produced in 1940 to meet a government demand for a test for color blindness obtainable in this country in sufficient quantity to supply all military testing stations. An instruction booklet was furnished, which has since proved to be inadequate and misleading, and no critical scores were supplied to differentiate between normal and defective color vision performance. In 1942 Gallagher, Gallagher and Sloane<sup>5</sup> made a critical evaluation of the individual plates of this test, after having found that only a small percentage of 726 male adolescents gave the correct response to every plate, that a large number failed more than 10 per cent of the plates and that a variety of responses was made to the same plate by persons with apparently normal color vision. The result was that the diagnosis as to the color vision of many subjects was in doubt. This has been the general experience of others who have administered this series of plates in the military services, in industry and in schools. For example, in our examination of 365 subjects whose color vision by other tests was judged to be normal, 95 per cent failed to read all the plates correctly, 46 per cent failed 6 or more of the plates, and 14 per cent failed 10 or more.<sup>6</sup> Rarely was there complete failure to see a digit, such as

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5. Gallagher, J. R.; Gallagher, C. D., and Sloane, A. E.: A Critical Evaluation of Pseudo-Isochromatic Plates and Suggestions for Testing Color Vision, *Yale J. Biol. & Med.* **15**:79-98 (Oct.) 1942.

6. Hardy, L. H.; Rand, G., and Rittler, M. C.: A Screening Test for Defective Red-Green Vision, *J. Optic. Soc. America* **36**:610-614 (Oct.) 1946; *Arch. Ophth.* **38**:442-449 (Oct.) 1947.



usually occurs when color vision is defective. Rather, the usual type of error was a misreading of digits because of careless observation, such as 48 for 43 (plate 2), a misreading of the Stilling digits of German formation, such as 25 for 75 (plate 30), the reading of the "invisible" digits (plates 33 and 34) or the combining of part of the correct and part of the "color-blind" response in the Ishihara type plates, such as 20 for 29 (plate 11). It is now generally recognized that this compilation of pseudoisochromatic plates has little diagnostic value, owing in large part to the inclusion of so many plates likely to be misread because of factors other than defective color vision.

This fault makes it impossible to establish an error score that will differentiate between normal and defective color vision performance. For example, some of our observers whose color vision was judged to be defective by other accepted criteria failed as few as 10 plates, whereas some whose color vision was similarly judged to be normal failed as many as 17 plates. There is, thus, a range in error score from 10 to 17 within which the diagnosis as to color vision is in doubt.

In the work of Kaplan and Lynch, no validation of the American Optical Company's compilation seems to have been made, or any administration of the test to a nonpsychotic population. They mentioned "the weakness of chart tests including their failure to test color perception" and pointed out that "some features are especially difficult for disoriented mental patients." They recognized also that the "tests do not determine the exact gravity of the color defect." Nevertheless, they classified their subjects into four categories without identifying the criteria on which these categories are based. They stated<sup>1</sup>:

A small number of patients, practically all males, with an incomplete total color blindness, comprises the first group. They present a deficiency in the red-green sense together with a slight weakness in the blue-yellow sense. The greatest number of color defectives are in the second group. All of its members are simply red-green blind but they differ in grades of severity. The heading, color weakness, is descriptive of the third group. This category includes patients who have showed a genuine hesitancy or who have incorrectly read some few plates. . . . Individuals without color defect are placed in the fourth group.

On the basis of these vague criteria, they concluded that "compared with known normal values, psychotic individuals show a high incidence of color defect" and that "psychotic females are afflicted with partial color blindness in comparatively high numbers." In view of what has already been said of the many random errors made by nonpsychotic subjects whose color vision is normal, the test records of Kaplan and Lynch need to be restudied before their conclusions can be accepted.

In final evaluation of the studies made by Millard and Shakow and by Kaplan and Lynch, it should be pointed out that the latter made no

mention of the conditions of illumination under which the color tests were made, and that the former used what they call "adequate daylight conditions." The variability in the color composition of daylight from dominant yellow to dominant blue and the need for standardization and control of this aspect of the illuminant used with pigment test material have been emphasized by one of us (L. H. H.)<sup>7</sup> and others since 1931, at which time standard illuminants for this type of work were adopted by the International Commission on Illumination (ICI).<sup>8</sup> Without this control test conditions are not constant; therefore, critical scores cannot be established between normal and defective color vision performance, and the results of color tests cannot be evaluated and interpreted correctly.

## PRESENT INVESTIGATION

### MATERIAL AND METHODS

This study was conducted at the New York State Psychiatric Institute. Dr. William A. Horwitz, associate clinical psychiatrist of the institute, arranged for the tests and supplied the medical diagnoses of the patients. When only those patients who were willing to take the tests and able to complete the series were included, there were 235 psychotic subjects, 123 male and 112 female. Of the male subjects, the diagnosis of schizophrenia was made for 106, of manic-depressive psychosis for 11 and of involutional psychosis for 2; 4 had miscellaneous psychoses. In addition, 37 male subjects with psychoneuroses were tested, chiefly patients with anxiety hysteria and obsessive-compulsive and reaction-compulsive neuroses. Of the female subjects, the diagnosis of schizophrenia had been made for 105, of involutional psychosis for 4, of manic-depressive psychosis for 2 and of Pick's disease for 1. In addition, 17 female patients with psychoneuroses were tested, chiefly patients with anxiety hysteria.

*Conditions of Test Administration.*—The tests were administered individually. The closest commercial approximation to ICI Illuminant C available at the present time was used to provide the illumination. (ICI Illuminant C approximates a color temperature of 6,750° K. and represents average overcast skylight.) This was obtained from the combination of a 100 watt, gas-filled tungsten lamp (color temperature 2,848° K.) and a Macbeth daylight glass filter, the combination giving a color temperature of 6,700° K. The level of illumination on the test material was above 25 foot candles, and the testing distance was about 30 inches (75 cm.).

*Color Tests Employed.*—Two tests were administered to all the subjects: (a) the Ishihara test (fifth edition),<sup>9</sup> utilizing, in addition to the demonstration plate, the 12 plates designed to detect defective color vision in literate subjects, and (b) the American Optical Company's compilation of Pseudo-Isochromatic Plates,<sup>10</sup> utilizing the 40 plates also designed to detect defective color vision in literate

7. Hardy, L. H.: Standard Illuminants in Relation to Color Testing Procedures, *Arch. Ophth.* **34**:278-282 (Oct.) 1945.

8. Smith, T., and Guild, J.: The C.I.E. Colorimetric Standards and Their Use, *Tr. Optic. Soc.* **33**:73-134, 1931-1932.

9. Ishihara, S.: Tests for Colour-Blindness, ed. 5, Tokyo, Kanehara, 1925.

10. Pseudo-Isochromatic Plates for Testing Color Perception, Philadelphia, Beck Engraving Co., 1940.

subjects. In addition, when the presence of defective color vision was found or suspected, recourse was had to the Hardy-Rand-Rittler Polychromatic Plates<sup>11</sup> for verification of the diagnosis.

*Criteria Used to Diagnose Anomaly in Color Vision.*—Ishihara Test for Color-Blindness: Following the criterion established by us<sup>12</sup> for this test administered under Macbeth daylight illumination, the misreading of 3 or fewer of the 12 plates utilized was taken to indicate normal color vision, and the misreading of 5 or more of the plates, to indicate defective color vision.

American Optical Company's Compilation: As has been stated, we were unable to establish a critical score that would screen normal from defective color vision when all 40 plates of this compilation were used. When, however, certain 22 of the plates were discarded as worse than useless, i. e., misleading, we were able to establish such a score, utilizing the remaining 18 plates.<sup>6</sup> With this 18 plate selection, the misreading of 4 or fewer plates indicates color vision within normal limits and the misreading of 5 or more plates indicates defective color vision, provided the test is administered under Macbeth daylight illumination. For each subject tested, however, the error score was computed (a) on the 40 plate series which was used by Kaplan and Lynch and (b) on our revised selection of 18 plates.

TABLE 1.—*Incidence of Defective Color Vision Among the Psychotic and Psychoneurotic Subjects Tested\**

Group	Sex	Number of Patients Examined	Defective Color Vision	
			Number	Per Cent
All psychoses.....	M	123	10	8.1
Schizophrenia.....	M	106	10	9.4
Other psychoses.....	M	17	0	0.0
Psychoneurosis.....	M	37	3	8.1
All psychoses.....	F	112	2	1.8
Schizophrenia.....	F	105	2	1.9
Other psychoses.....	F	7	0	0.0
Psychoneurosis.....	F	17	0	0.0

\* Diagnosis as to defective color vision was based on the Hardy-Rand-Rittler criteria for the Ishihara test and the 18 plate selection from the American Optical Company's compilation and on the Hardy-Rand-Rittler Polychromatic Plates.

## RESULTS

A general statement of the results obtained follows. Of the 123 male psychotic patients, 10 (8.1 per cent), and of the 112 female psychotic patients, 2 (1.8 per cent), had defective color vision. Of the 37 male psychoneurotic patients, 3 (8.1 per cent) had defective color vision, and in the 17 female psychoneurotic patients no case of anomaly in color vision was found. All the patients were consistently classified as to normal or defective color vision by our criterion for the Ishihara test and by our criterion for the 18 plate selection from the American Optical Company's compilation. The results are shown in table 1.

11. Hardy, L. H.; Rand, G., and Rittler, M. C.: Color Vision and Recent Developments in Color Vision Testing, *Arch. Ophth.* **35**:603-614 (June) 1946.

12. Hardy, L. H.; Rand, G., and Rittler, M. C.: Tests for Detection and Analysis of Color Blindness: I. An Evaluation of the Ishihara Test, *Arch. Ophth.* **34**:295-302 (Oct.) 1945.

As is seen in table 1, all the psychotic patients with the diagnosis of defective color vision belonged in the large group of schizophrenic patients. The incidence of defective color vision for the male schizophrenic subjects was 9.4 per cent, and that for the female schizophrenic subjects, 1.9 per cent. The question arises whether these figures furnish evidence of a higher incidence of defective color vision in the schizophrenic groups than would be found in normal groups of the same size.

Accepting 8 per cent as the incidence of defective color vision in the normal male population, we find from computation from the normal curve that the magnitude of the difference found by us (1.4 per cent) is such that it could have been equaled or exceeded 60 per cent of the time in chance samples of 106 subjects. For this reason, the incidence of 9.4 per cent found in our schizophrenic group has no statistical significance and would be expected from chance factors alone.

The incidence of defective color vision in the normal female population (0.5 per cent) lies in the realm of small samples—the Poisson realm. Calculation of the Poisson distribution shows that an incidence of anomaly in color vision of 1.9 per cent could be equaled or exceeded 10 per cent of the time by chance variation. There appears, then, to be no statistical significance in the incidence of defective color vision found in our female schizophrenic group.

From the results of our study we conclude, therefore, that in the general group of psychotic patients tested by us, as well as in the special group of schizophrenic patients, there is no significantly higher incidence of anomaly in color vision than would occur in nonpsychotic groups of the same size. This conclusion is in agreement with that of Millard and Shakow and in disagreement with that of Kaplan and Lynch.

In the attempt to see whether there are any differences of note between the responses to pseudoisochromatic tests made by nonpsychotic patients and the responses made by psychotic patients, and to offer an explanation, at least in part, of the conclusion reached by Kaplan and Lynch, an analysis was made of the number of errors and the individual plates failed by members of our psychotic group and by nonpsychotic subjects whom we had examined under the same conditions with the Ishihara test and with the American Optical Company's compilation of color plates.

*Ishihara Test.*—On this test we have for comparison the records of 71 nonpsychotic and 223 psychotic subjects whose color vision was judged normal. Table 2 shows the number of plates failed by the members of each sex in each group and by each group as a whole. It is seen in this table that the range of error scores is the same for the nonpsychotic and for the psychotic group and that the distribution of error scores is quite similar, with the exceptions that fewer of the psychotic patients made a perfect score and more failed one or two plates

(columns 4 and 7). A comparison of columns 2 and 5, which give the distribution of errors made by the male subjects of each group, and of columns 3 and 6, which give this distribution for the female subjects, shows that the greater number of errors made by the psychotic group as a whole was due almost entirely to the tendency of the psychotic female patients to make many more random errors than were made by the nonpsychotic female subjects. The distribution of errors for the male subjects of the two groups is very similar.

An analysis of the individual plates of the Ishihara test failed by the members of the two groups who had normal color vision showed that plates 5, 10 and 11 were most frequently failed. Plate 5 was misread by 27 per cent of the nonpsychotic and by 35 per cent of the psychotic group. Instead of 74, the number was most often read as 71. Other responses were 24, 91, 11 and 21. The color-blind response 21 was given by 6 per cent of each group. It is our experience that this

TABLE 2.—*Results for Ishihara Test (Fifth Edition), Showing for Comparison Number of Plates Failed by 71 Nonpsychotic and 223 Psychotic Subjects All of Whom Were Judged to Have Normal Color Vision\**

Number of Plates Failed	Nonpsychotic Group			Psychotic Group		
	Males (33), per Cent	Females (38), per Cent	Total (71), per Cent	Males (113), per Cent	Females (110), per Cent	Total (223), per Cent
0	45.5	63.2	54.9	46.9	38.2	42.6
1	33.3	23.7	28.2	36.3	39.1	37.7
2	18.2	10.5	14.1	13.3	20.0	16.6
3	3.0	2.6	2.8	3.5	2.7	3.1

\* The 12 plates designed to test color vision among literate subjects were used.

single color-blind response is not evidence of defective color vision provided it is the only typically color-blind response, excluding those to plates 10 and 11, on which plates some pattern was frequently seen by members of each group.

Finally, we have for comparison on the Ishihara test the records of 74 nonpsychotic and of 12 psychotic subjects whose color vision was judged to be defective. The range of error scores for the former group was 5 to 12<sup>13</sup> and for the latter group 7 to 12.

13. It may be of interest to note that the criterion of Miles and the Worcester III criterion of Millard and Shakow were also applied to the test records of our psychotic and nonpsychotic subjects of both the groups with normal and the groups with defective color vision. The criterion of Millard and Shakow gave a diagnosis as to color vision that was consistent in every case with our own. On the Miles criterion, however, 4 additional members (6 per cent) of the nonpsychotic group, 3 male and 1 female subjects, and 6 additional members (3 per cent) of the psychotic group, 3 of each sex, would have been rated as having defective color vision.

*American Optical Company's Compilation (40 Plates).*—On this test, we have for comparison the records of 365 nonpsychotic and 223 psychotic subjects whose color vision was judged to be normal. Table 3 shows the number of plates failed by each sex of each group and by each group as a whole. As was the case in table 2, table 3 also shows that the range of error scores is the same for the nonpsychotic and for the psychotic group and that the distribution of error scores is, with minor exceptions, very similar (columns 4 and 7). For each group the maximum error score was 17, and the median error score, 5. A comparison of the distribution of errors for the two groups for each sex considered separately shows even more strikingly than in the Ishihara test that the psychotic female subjects made many more random errors than the nonpsychotic female subjects.

TABLE 3.—*Results for American Optical Company's Compilation of Pseudo-Isochromatic Plates, Showing for Comparison Number of Plates Failed by 365 Nonpsychotic and 223 Psychotic Subjects All of Whom Were Judged to Have Normal Color Vision\**

Number of Plates Failed	Nonpsychotic Group			Psychotic Group		
	Males (222), per Cent	Females (143), per Cent	Total (365), per Cent	Males (113), per Cent	Females (110), per Cent	Total (223), per Cent
0 or 1	7.2	18.9	12.6	12.4	8.2	10.3
2 or 3	16.7	25.2	18.4	29.2	20.0	24.7
4 or 5	25.2	19.6	23.0	22.1	20.0	21.1
6 or 7	19.8	16.0	19.2	15.0	20.0	17.5
8 or 9	16.7	7.0	13.0	8.9	10.0	9.4
10 or 11	6.8	7.0	7.1	7.1	14.5	10.8
12 or 13	4.9	4.9	4.4	3.5	0.9	2.2
14 or 15	1.8	1.4	1.7	0.9	2.7	1.8
16 or 17	0.9	0.0	0.6	0.9	3.6	2.2

\* The 40 plates designed to test color vision among literate subjects were used.

An analysis of the individual plates of this test failed by the members of each group who had normal color vision showed nothing of significance, with the possible exception that more of the psychotic group tended to see part of the "color-blind" number on Ishihara type plates 11 and 12 and more tended to see some pattern on the "invisible digit" plates 33 and 34. In general, however, the plates that were failed by a comparatively high percentage of the nonpsychotic group were failed also by a high percentage of the psychotic group, and those that were failed by a low percentage of the nonpsychotic group were similarly failed by a low percentage of the psychotic group.

A comparison of the number of plates failed by the 117 nonpsychotic subjects and the 12 psychotic subjects having defective color vision shows that the range of error scores for the former group was 10 to 38,<sup>6</sup> and that for the latter group, 10 to 39.,

Chart 1 shows the distribution of the number of plates failed on the 40 plate compilation for both the subjects with normal and the subjects with defective color vision in the nonpsychotic and in the psychotic group tested by us. In this chart, rectangles in outline present the data for subjects whose color vision was judged to be normal; black rectangles, data for subjects whose color vision was judged to be defective. Data for the nonpsychotic group are given in the left hand rectangles, and data for the psychotic group, in the right hand rectangles. For reader identification, the rectangles which present the data for the psychotic group are striped diagonally, black on white indicating normal color vision and white on black indicating defective color vision. The number of plates failed (error score), in steps of 2, is

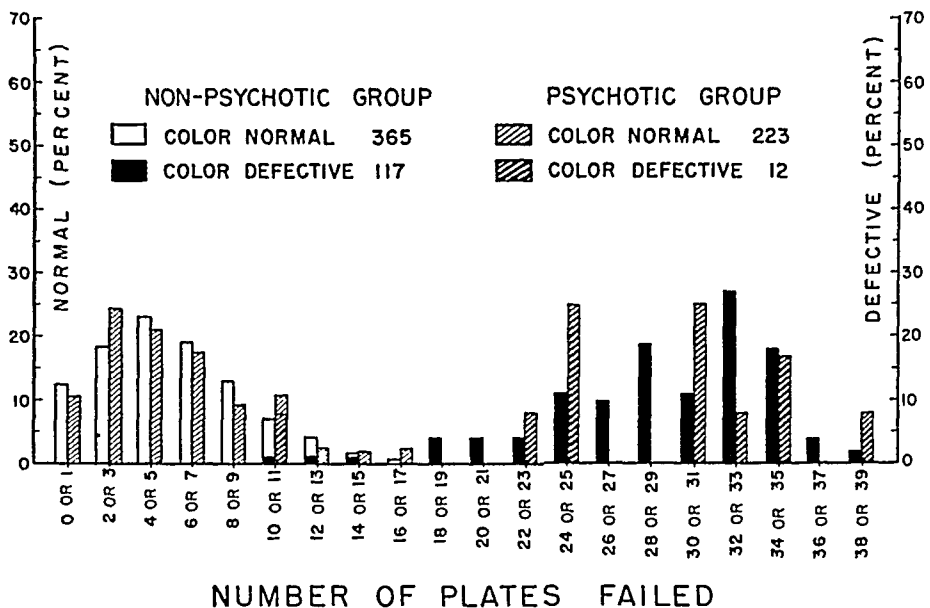


Fig. 1.—Distribution of number of plates failed in the American Optical Company's compilation of 40 Pseudo-Isochromatic Plates for subjects with normal and for subjects with defective color vision in both the nonpsychotic and the psychotic group.

plotted on the horizontal coordinate, and the percentage of cases, on the vertical coordinate. Chart 1 clearly shows the general similarity of the distributions of error scores for the two groups of subjects with normal color vision. It also shows for both groups the same overlapping range of 10 to 17 errors within which the diagnosis of normal or defective color vision is in doubt.

In concluding the discussion of this test, we wish to say that, in our opinion, the observation by Kaplan and Lynch of a high incidence of defective color vision among psychotic subjects was in major part due (a) to poor selection of the test for color blindness used in the study, (b) to ignorance of the many random errors which nonpsychotic sub-

jects whose color vision is normal make on this test and (c) to inadequate criteria on which to base the diagnosis of defective color vision. Lack of control of conditions under which the test was administered may also have been a contributing factor.

TABLE 4.—*Results for American Optical Company's Compilation (18 Selected Plates), Showing for Comparison Number of Plates Failed by 365 Nonpsychotic and 223 Psychotic Subjects All of Whom Were Judged to Have Normal Color Vision*

Number of Plates Failed	Nonpsychotic Group			Psychotic Group		
	Males (222), per Cent	Females (143), per Cent	Total (365), per Cent	Males (113), per Cent	Females (110), per Cent	Total (223), per Cent
0	66.1	81.2	72.0	65.5	67.3	66.4
1	25.3	15.3	21.4	24.8	20.0	22.4
2	4.1	2.8	3.6	8.0	6.5	7.2
3	3.2	0.7	2.2	1.7	5.4	4.6
4	1.3	0.0	0.8	0.0	0.9	0.4

TABLE 5.—*Results for American Optical Company's Compilation (18 Selected Plates), Showing for Comparison Percentage of Nonpsychotic and Psychotic Group Having Normal Color Vision Who Failed Each Plate of This Selected Series\**

Plate Number	Nonpsychotic Group			Psychotic Group		
	Males (222), per Cent	Females (143), per Cent	Total (365), per Cent	Males (113), per Cent	Females (110), per Cent	Total (223), per Cent
3	1.8	0.7	1.4	0.0	1.8	0.9
4	5.0	1.4	3.6	0.9	4.5	2.7
5	0.0	0.0	0.0	0.9	0.0	0.5
6	0.0	0.0	0.0	0.0	0.0	0.0
8	11.3	3.5	8.2	2.7	6.3	4.5
9	0.5	0.0	0.3	0.9	0.0	0.5
12	8.1	4.2	6.6	18.6	12.7	15.7
13	0.5	0.0	0.3	0.0	3.6	1.8
16	0.0	0.0	0.0	0.0	0.0	0.0
17	4.5	2.1	3.6	3.5	5.5	4.5
19	0.0	0.0	0.0	0.0	0.0	0.0
20	2.3	0.7	1.6	5.3	7.3	6.3
21	5.4	2.8	4.4	2.7	7.3	4.9
23	1.8	1.4	1.6	0.9	0.9	0.9
27	3.2	2.8	3.2	3.5	3.6	3.6
29	1.4	2.1	1.6	3.5	1.8	2.7
41	0.0	0.0	0.0	0.9	0.0	0.5
42	9.0	0.0	5.5	3.5	0.9	2.2

\* Each plate is designated by the number of its occurrence in the full compilation.

*American Optical Company's Compilation (18 Selected Plates).—*On this test we, again, have for comparison the records of 365 nonpsychotic and 223 psychotic subjects whose color vision was judged to be normal. Table 4 shows the number of plates of this series failed



by each sex of each group and by each group as a whole. Once more, the same similarities are shown between the nonpsychotic and the psychotic group as were seen in tables 2 and 3, that is, (a) the same range of error scores, (b) the same median error scores and (c) the general similarity in distribution of errors, with the exception of the tendency of the psychotic group to make more errors. This tendency is much less pronounced in this selection of 18 significant plates than it was in the full 40 plate compilation, and once more we find it was mainly due to the greater number of errors made by the psychotic female subjects.

Table 5 shows the plates used in this selected series and the percentage of each sex of each group and that of each group as a whole who

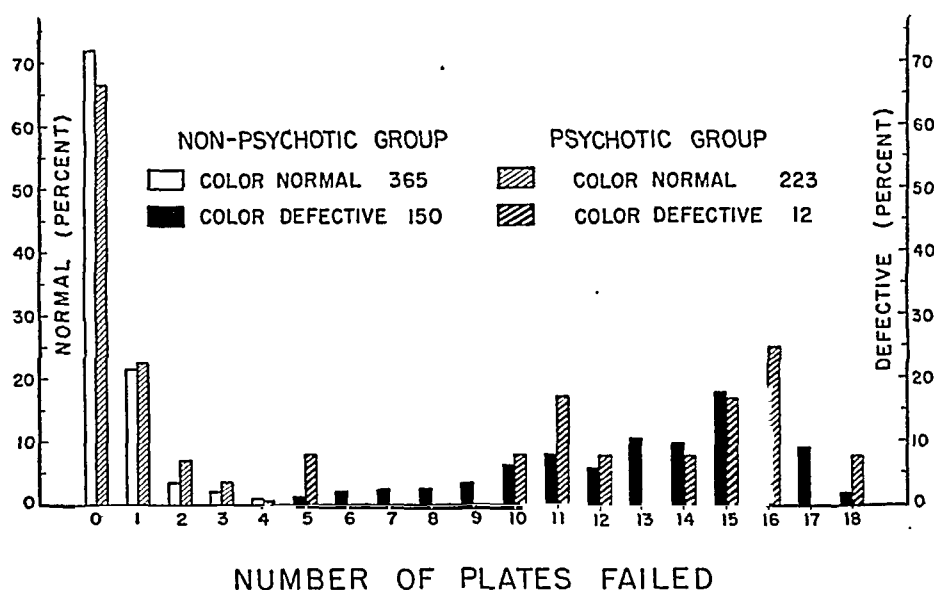


Fig. 2.—Distribution of error scores on the 18 plate selection of the American Optical Company's Pseudo-Isochromatic Plates for subjects with normal and for subjects with defective color vision in both the nonpsychotic and the psychotic group.

failed each plate. The plates are designated by the number of their occurrence in the American Optical Company's full compilation. The table shows little difference of significance between the responses of the groups compared, except for the responses to plate 12 already noted in the previous section and the higher percentage of errors made by the psychotic female subjects.

A comparison of the number of plates of this selected series which were failed by 150 nonpsychotic and the 12 psychotic subjects having defective color vision shows that the range of error scores for both the former and the latter group was 5 to 18.<sup>6</sup> It is thus seen that the critical score established for this series on a nonpsychotic group to

differentiate between normal and defective color vision performance holds for the psychotic group as well.

In chart 2 is shown the distribution of error scores on the 18 plate selection for both the subjects with normal color vision and the subjects with defective color vision in the nonpsychotic and psychotic groups. The data are presented in the same form as in chart 1. Chart 2 shows (a) the general similarity in the distribution of error scores for the two groups with normal color vision and (b) the same range of error scores for these groups when color vision is normal and when it is defective. In other words, in both groups with normal color vision no more than 4 plates were failed, and in both groups with defective color vision no fewer than 5 plates were failed.

### CONCLUSIONS

The incidence of color blindness among the psychotic patients tested by us was not significantly higher than that among the normal population.

In our opinion, the contrary finding by Kaplan and Lynch was in major part due (a) to poor selection of the test for color blindness used in their study, (b) to ignorance of the many random errors made on this test by nonpsychotic subjects whose color vision is normal and (c) to inadequate criteria on which to base the diagnosis of the presence of defective color vision. Lack of control of conditions under which the test was administered may also have been a contributing factor.

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## PREPLACEMENT OF AIR IN CYCLODIALYSIS

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THE ADVANTAGES of the use of air after cyclodialysis have been fully discussed by Barkan<sup>1</sup> and several other writers in recent articles.<sup>2</sup> These advantages were summarized by Barkan as follows: The injection of air (1) controls hemorrhage, (2) widens the cyclodialysis cleft, (3) makes the cleft visible and (4) deepens the anterior chamber. He stated:

Cyclodialysis combined with air injection is indicated in primary glaucoma of the wide angle type. It is especially indicated, to the exclusion of trephination, iridencleisis and iridectomy in the late stage of the narrow angle type after peripheral adhesions have closed the angle in large part, irrespective of whether there is congestion or not. It is indicated in those varieties of secondary glaucoma in which cyclodialysis is commonly accepted as being indicated, [e. g., aphakia]. . . . A high degree of pressure has not contraindicated its use.

In all the methods described in the literature the air is injected after the completion of the dialysis. For the past year we have routinely injected air into the anterior chamber as the first step in the operation, before the scleral incision for the cyclodialysis. This procedure was used originally in a case in which the anterior chamber was almost completely obliterated, in order to deepen the chamber. The lens-iris diaphragm was thus pushed backward, safely out of the way of the spatula.

Since then, cyclodialysis preceded by the injection of air has been performed on 9 eyes. The patients were private ones and were followed closely both before and after operation. In all cases the tension after operation was under 25 mm. (Schiotz), continuously, although pilocarpine was required in 4 cases. The visual acuity and visual fields were maintained without loss in every case.

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1. Barkan, O.: Cyclodialysis, Multiple or Single with Air Injection: An Operative Technique for Chronic Glaucoma, *California Med.* **67**:78 (Aug.) 1947.

2. (a) Randolph, M. E.: A New Cyclodialysis Instrument, *Am. J. Ophth.* **26**:187 (Feb.) 1943. (b) Shaffer, R. N.: Inverse Cyclodialysis, *ibid.* **30**:860 (July) 1947. (c) Sugar, H. S.: Cyclodialysis: A Follow-Up Study, *ibid.* **30**:843 (July) 1947.

This modification of injecting air before the cyclodialysis incision, instead of after the operation, is an important one. It retains all the advantages of injecting air after operation. In addition, it prevents hemorrhage by avoiding sudden loss of intraocular pressure, since the preplaced air expands, replacing the volume of aqueous lost.

The hemorrhage most frequently occurs immediately on dialysis. A certain amount is already present before the spatula can be withdrawn and air injected. In other words, the postoperative injection of air arrests an already forming hemorrhage. Any blood present has a tendency to close the cleft, form synechias and thus nullify the operative result. Preoperative injection of air provides a cushion of air under slight pressure, which tends to prevent any bleeding at all; especially at the crucial moment of dialysis. The preoperative injection of air also deepens the anterior chamber and keeps it deep throughout the procedure. The iris is kept out of the way of the spatula by the air bubble. There are thus more room for the dialysis and less danger of injuring lens or iris and of peeling off Descemet's membrane, since the cornea does not have to be hugged as closely. As has been shown by Hughes and Cole,<sup>3</sup> air in the anterior chamber enables the angle of the chamber to be visualized without a contact lens. By preplacement of air, the angle and the cleft can be visualized during the entire procedure.

Technically, it is far easier to inject air into the anterior chamber before the operation, and there is far less risk. When the air is injected after operation, the eye is soft. The needle is inserted through a long tract, with only choroid separating it from the vitreous beneath. As Shaffer<sup>2b</sup> observed, there is always the possibility of puncturing the choroid or of the choroid herniating through the wound as the air pressure is increased.

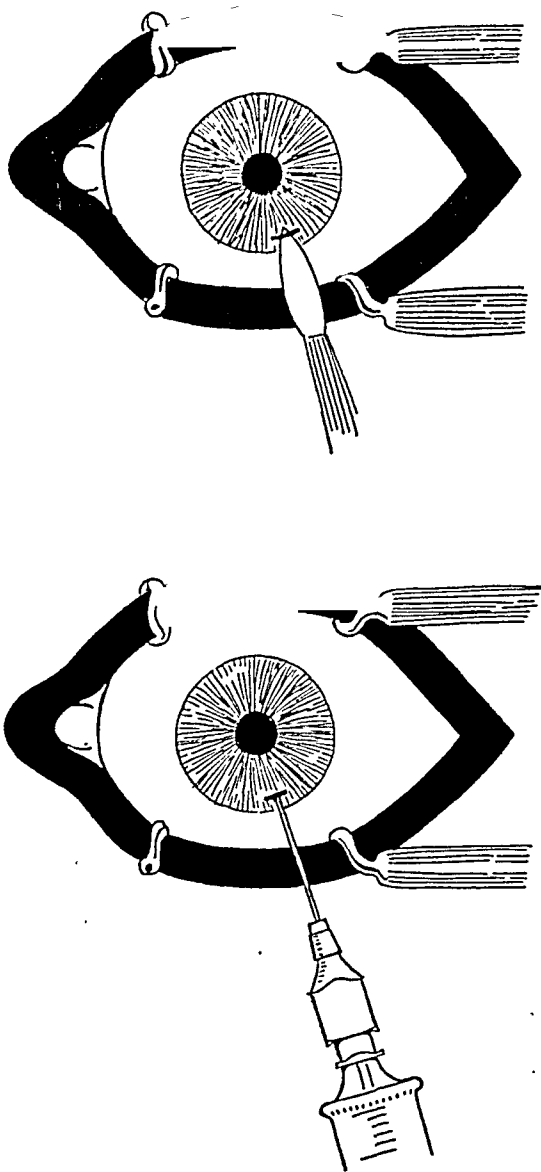
#### PROCEDURE

The cornea is punctured at the limbus in the lower outer quadrant with either a Graefe knife or a small keratome. The point should pass just to Descemet's membrane, so that the aqueous does not escape. Air is drawn into a dry 2 cc. Luer syringe with a small hypodermic needle, 26 gage, attached. The needle is then inserted into the preformed opening, following the track of the previous incision. No aqueous is withdrawn. Approximately 1.5 cc. of air is injected into the anterior chamber. Enough is injected so that the iris is pushed back and the chamber is almost completely occupied by the air bubble. A narrow ring of aqueous usually remains at the limbus, sometimes in the form of small bubbles. The usual cyclodialysis is done in the upper outer quadrant, provided gonioscopic inspection shows no contraindication to this site. In sweeping the spatula, care must be taken not to pull up on the heel of the instrument. This

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3. Hughes, W., and Cole, J.: Technical Uses of Air in Ophthalmology, *Arch. Ophth.* 35:525 (March) 1946.

creates a vacuum along the tract, and the air in the anterior chamber is sucked out through the wound opening. The sweeping motion should be made with the tip of the spatula held against the sclera and the heel left in place as the fulcrum. There is a tendency, in trying to keep the tip of the spatula hugging the sclera, to pull up on the heel of the instrument. This should be avoided.



Upper figure, keratome incision at lower portion of limbus, just to Descemet's membrane; lower figure, insertion of needle through preformed track.

Immediately after withdrawal of the spatula the globe is compressed for a few minutes with two applicators, one at the scleral wound and one at the opposite portion of the limbus—at 8 o'clock if the incision is at 2 o'clock.

Physostigmine is instilled after operation. The head of the bed is kept elevated continuously at an angle of 35 degrees, so that the air bubble rests against the cleft.

In all but 1 case, in which the air was lost through the cyclodialysis opening because of pulling up on the heel of the spatula, there was no, or almost imperceptible, bleeding, either immediate or late.

#### SUMMARY

Preplacement of air in cyclodialysis offers the following advantages over postplacement:

1. It is technically easier and safer.
2. It prevents hemorrhage, instead of arresting bleeding which has already commenced.
3. It facilitates the dialysis, especially in shallow chambers.
4. It allows visibility of the angle and of the cleft throughout the entire procedure.
5. There seem to be no contraindications.

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## DEEP KERATITIS ASSOCIATED WITH ATYPICAL LICHEN PLANUS

Report of a Case

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**R**ECENT studies<sup>1</sup> have shown that there is a close relation between prolonged quinacrine ("atabrine") medication and the development of cutaneous lesions bearing a striking resemblance to classic lichen planus. Because of this resemblance, the name "atypical lichen planus" was designated as the most appropriate term for the disease. It is my opinion that both the quinacrine medication and the subsequent cutaneous lesions played an important role in the production of the keratitis.\* This belief will be elaborated on later.

In all the literature dealing with this disease and in a personal observation of over 250 cases, only 1 case was encountered in which the deeper layers of the cornea were affected. This ocular involvement was particularly interesting not only because of its rarity but because of its close relation to the course of the cutaneous disease. It appeared during the height of the cutaneous disturbance and subsided in a manner closely paralleling the resolution of the dermatologic condition. The only other ocular lesions sometimes, though infrequently, seen in association with atypical lichen planus were blepharoconjunctivitis, conjunctivokeratitis and cutaneous lesions of the eyelids. Atypical lichen planus<sup>2</sup> is a new dermatologic entity, first seen during World War II. The cutaneous lesions have been classified as (1) atypical lichen planus, (2) atypical lichen planus with eczematoid characteristics and (3) eczematoid dermatitis. The first two types were observed only after prolonged ingestion of quinacrine. The third type seemed to be an acute allergic response to a single dose of quinacrine and

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From the Department of Ophthalmology, Mount Sinai Hospital.

Read at a meeting of the New York Society for Clinical Ophthalmology, New York, Feb. 3, 1947.

1. Bazemore, J. M.; Johnson, H. H.; Swanson, E. R., and Hayman, J.: Relation of Quinacrine Hydrochloride to Lichenoid Dermatitis (Atypical Lichen Planus), *Arch. Dermat. & Syph.* **54**:308-324 (Sept.) 1946.

2. Rosenthal, J.: Atypical Lichen Planus (Southwest Pacific), *Am. J. Path.* **22**:473-491 (May) 1946. Dantzig, L., and Marshall, L. E.: Tropical Lichen Planus (New Guinea Variety): Clinical Report on Twenty-Four Cases (Possible Role of Quinacrine), *New York State J. Med.* **46**:991-995 (May 1) 1946.

occurred after an interval of several minutes to one week. More than one-half the patients showed two of the three types coexisting. In the Southwest Pacific area this disease became the most frequent cause of evacuation of patients with disabling cutaneous diseases.

#### REPORT OF CASE

*History.*—M. J., a white man aged 34, sergeant in the Army of the United States, had been in India since October 1944, after eight months' duty in New Guinea. Having received 55 Gm. of quinacrine hydrochloride U.S.P. as suppressive therapy since January 1944, he presented dryness and cracking of the skin involving the palms and fingers of both hands in May 1945, sixteen months later. The lesions extended along both forearms. The involvement of the skin was characterized by a purplish discoloration and a mild degree of itching. Shortly afterward, both legs and the external ears became involved in a similar manner. These lesions soon began to manifest a tendency to weep. He was hospitalized on July 3, 1945 at the 198th General Hospital and complained of blurred vision for the first time on Sept. 1, 1945, four months after the onset of the cutaneous disease. After continuous hospitalization for a number of weeks, with no definite response to therapy, he was returned to the United States and was transferred to the Battey General Hospital, arriving there on Sept. 30, 1945. The family and past histories were noncontributory. He denied having had venereal disease.

*Physical Examination.*—The normal weight was 180 pounds (81.8 Kg.); the present weight, 154 pounds (70 Kg.). The femoral, posterior cervical and auricular lymph nodes were enlarged. The oral mucosa was clear. The heart and lungs were normal. The blood pressure was 130 systolic and 74 diastolic. A roentgenographic study of the chest, examinations of the stool, blood count, urinalyses, serologic tests, malarial smears and hepatic function tests all gave results within normal limits. The skin in general was ichthyotic. There was a moth-eaten type of alopecia with multiple coin-sized, lavender, scaly patches on the scalp and similar-sized erythematous, atrophic areas. The pinnae and the external auditory canals were involved in an eczematoid process, with fissuring, and were swollen from a secondary infection. The ear drum membranes were intact. There was some scaling on the face, and the upper eyelids showed small, superficial patches of lavender, scaling dermatitis. Larger patches of the same type were present on the neck, in the axilla and in the crotch, but these areas were secondarily eczematized. Extending from above both knees, a diffuse eczematoid, weeping process spread along the dorsal aspect of the feet to the toes. The hands, dry and scaling, had a peculiar violaceous hue.

*Ophthalmologic Study.*—Vision was 20/70 in the right eye and could not be improved with a +0.50 D. sphere, and was 20/20 in the left eye. Associated movements were full in all the cardinal directions. No muscular imbalance was noted. The right pupil was round and regular and reacted sluggishly to light and fairly well in accommodation; the left pupil responded normally. Intraocular tension appeared to be within normal limits on digital palpation. A slight circumcorneal flush was present in the right eye. Conjunctival lesions were searched for, but none was found. A faint, circular, diffuse haze with irregular margins, measuring approximately 5 mm. in diameter, was observed by sclerotic scatter within the pupillary area of the cornea (fig. 1). On examination with direct illumination, moderate swelling of the cornea centrally could be seen. This manifested itself by a bulging of the posterior part of the optic section toward the anterior chamber. Optic dissection of the tissues corresponding to this region



of the cornea, from anterior to posterior, revealed the following condition: The epithelial surface was smooth and clear. Bowman's membrane and the anterior half of the substantia propria appeared within normal limits. Several tissue clefts of varying sizes were present in the swollen posterior layers, which showed a moderate increase in reluctance and many small, discrete, faint gray spots. Despite these, a number of folds in Descemet's membrane and a cluster of needle-shaped crystals plastered on the endothelium could be observed without difficulty. A polychromatic luster was reflected from the crystals when the beam from the slit lamp was shifted from side to side. A large number of precipitates, varying in

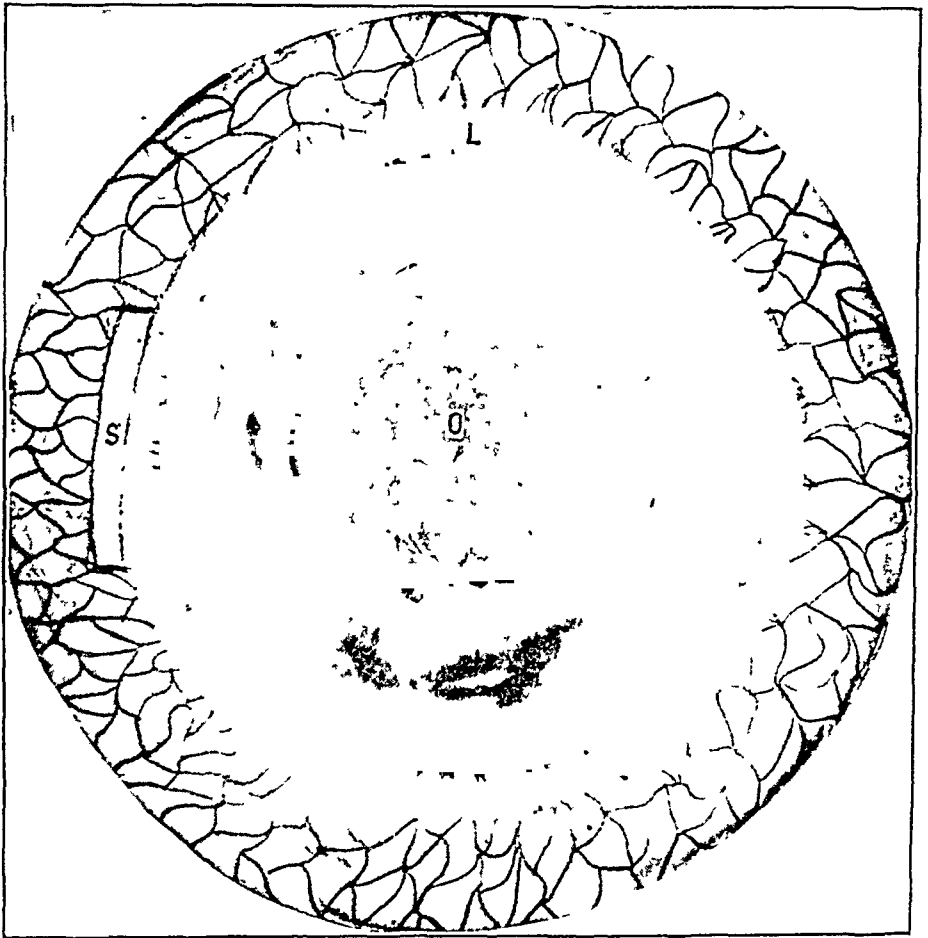


Fig. 1.—Sclerotic scatter, demonstrating (O) large central opacity of the right cornea, (S) beam of the slit lamp and (L) limbal glow.

size and shape, were strewn on and about the crystals. These deposits varied from gray to light brown. They decreased in number peripherally. The circular border of the interstitial infiltration extended to a zone about 3 mm. from the limbus, leaving a clear, circular band of cornea. In the right eye on upward gaze, a 2 plus aqueous flare was observed through the clear cornea. No posterior synechias were seen. The fundus could not be visualized through the undilated pupil. After its dilation, a sprinkling of fine cells was visible on the anterior capsule of the lens. No lenticular changes were noted. The fundus and vitreous appeared within normal limits. The left eye revealed no pathologic changes.

*Diagnosis.*—The diagnosis was (1) atypical lichen planus, with severe eczematoid characteristics; (2) keratitis of the right eye, acute, moderate, deep and probably secondary to the cutaneous disease, and (3) iritis of the right eye, moderate, low grade and secondary to the keratitis.

*Subsequent Course.*—On October 6, three months after his admission, reexamination revealed a slight increase in activity in the right eye. The cornea appeared more edematous, and there was an increased deposition of cellular elements on the endothelium. The substantia propria in proximity to Bowman's membrane showed an early increase in relucence. Twelve days later it was observed that the



Fig. 2.—Optic section of figure 1, active stage. *E* indicates epithelial vesicle; *B*, folds in Bowman's membrane; *C*, tissue clefts, increased relucence and bulging of the posterior layers of the cornea; *D*, folds in Descemet's membrane and keratic precipitates and crystals on the endothelium; *A*, cells and fibrinous exudate in the anterior chamber.

corneal opacity had extended peripherally, approximately 1 to 2 mm. The bulbar injection had become more intense. Up to that time, the pathologic process had been localized principally to the posterior layers of the cornea. On this examination, however, it was found that the epithelial surface overlying the deep infiltration presented a number of small vesicles, varying in size from 1 to 2 mm. in diameter (fig. 2). Two of these vesicles appeared to have been broken recently, since one could easily discern their ragged and filamentous edges after they had been

stained with a 2 per cent solution of fluorescein sodium U.S.P. Bowman's membrane and the anterior third of the cornea showed a moderate increase in the number and degree of relucet areas, and several tissue clefts were present. The parenchymatous infiltration had become so pronounced that the details in the posterior layers could be demonstrated only with great difficulty. The aqueous flare was 4 plus, and the details of the fundus were obscured. Neither anterior nor posterior synechias could be found. Digital palpation of the right eye at this time gave no evidence of increased intraocular tension. The patient complained only of a persistent, dull, aching pain in the right eye.

Most of the cutaneous lesions slowly regressed under treatment, but several areas remained active and became excoriated, especially at night and in the morning. This excoriation was attended with increased weeping of the lesions. Roentgen treatment was ordered on October 27, to control the pruritis of the lower extremities. Additional local treatment consisted in use of cool compresses to the legs, alternating with the application of soothing ointments. This therapy was intended to combat the eczematoid component. Further improvement of the skin followed three intravenous injections of typhoid vaccine, beginning on Oct. 26, 1945, together with a decreased activity of the corneal infiltration. At this point, the dermatologist advised the transfer of the patient to a skin center, in view of the necessity for the continued treatment of both the skin and the eye.

Accordingly, on November 8, the patient was admitted to Moore General Hospital. The diagnosis of atypical lichen planus with eczematoid characteristics was confirmed by Lieut. Col. James M. Bazemore, chief of the skin center. It was further noted that the mucous membrane of the mouth was the site of lacelike lesions, typical of the disease. Further examination of the right eye disclosed the following picture: Vision was 20/50, uncorrectible. The eye showed slight ciliary injection with conspicuous bedewing of the epithelium immediately anterior to the circumscribed area of infiltration in the posterior layers of the stroma. Numerous folds were present in Descemet's membrane. A striking increase of keratic precipitates was noted. The pupil was well dilated and free of posterior synechias. The anterior capsule of the lens was strewn with fine white dots and with spots of brown pigment. The lens and vitreous were within normal limits. The left eye was normal.

The patient was given four more intravenous injections of typhoid vaccine, beginning November 15. The corneal bedewing and the circumcorneal flush were gone by November 30. The increased reluctance of the posterior layers began to lessen, the folds of Descemet's membrane to flatten and the precipitates to clear to such a degree that the details of the iris could be made out more clearly. The edema of the center of the cornea became absorbed to such an extent that the cornea resumed almost its natural thickness.

The patient was given urologic clearance on November 23. Examination of the feces disclosed no ova or parasites. The serologic reactions were negative on November 29. Study of the blood demonstrated 5,050,000 red cells, 100 per cent hemoglobin and 5,600 white cells, with 56 neutrophils, 35 lymphocytes, 4 monocytes, 4 eosinophils and 1 basophil. Intracutaneous tests with purified protein derivative of tuberculin U. S. P. gave negative reactions in two dilutions. A roentgenogram of the paranasal sinuses revealed no abnormalities.

Since the condition of the right eye and that of the skin had shown such great improvement, the patient was granted a sixty day convalescent furlough. He returned to the hospital on Feb. 24, 1946, in excellent condition and spirits. The hair of the scalp had grown in almost completely except for some irregularity of the hair line over the temples and on the back of the head. A number of discrete, poliotic patches were present throughout the scalp, in proximity to small, round

or oval, slightly raised, purplish plaques, which showed evidence of scaling. The returning hairs were strong and not easily removed from the dry scalp. The skin of the upper portion of the forearms and the lower parts of the legs revealed the regressive changes characteristic of subsiding atypical lichen planus. These changes consisted of discrete, purplish macules of varying sizes and shapes, hyperpigmentation, vitiligo and slight atrophy of the skin.

At this time, examination of the right eye gave interesting results. Vision was 20/15 in the right eye and 20/20 in the left eye. There was no bulbar injection. The epithelial surface was smooth and clear. The swelling of the central



Fig. 3.—Optic section, healed stage. *S* indicates Stähli-Hudson line; *C*, several tissue clefts and faint relucence; *EA*, cells and keratic precipitates, which were occasionally seen.

parenchyma of the cornea had receded (fig. 3). Sclerotic scatter demonstrated the complete disappearance of the circumscribed corneal infiltration. A thin, horizontal Stähli-Hudson line, measuring 5 mm. in length, was seen 4 mm. above the lower limbus. Several tissue clefts were still found, but the relucet areas in the anterior, and especially in the posterior, layers of the cornea had faded out almost completely. No folds in Descemet's membrane could be discerned. A small number of fine precipitates, the majority of them colorless, still remained on the endothelial surface. An occasional cell floated in the anterior chamber. The iris, in middilatation, showed no posterior synechias. The fine deposits

on the anterior capsule of the lens had cleared up, so that it was now possible to see three congenital V-shaped pigment spots. The lens and the vitreous were clear. The fundus was normal.

It was apparent that the administration of penicillin, both intramuscularly and locally, to the eye in the form of drops and ointment had in no way altered the course of the keratitis, and that the direct application of sulfadiazine powder to the cornea had likewise proved ineffective.

Since the eye had recovered so satisfactorily, it was decided that the patient could be discharged on the basis of the condition of his skin. On March 8, 1946 he received a certificate of disability discharge and was instructed to present himself to the outpatient department of a veterans facility for further observation.

#### COMMENT

The atypical lichen planus observed during World War II resembled in the basic morphologic changes the classic lichen planus but, in addition, presented many unusual features. Poliosis, hyperpigmentation, vitiligo and alopecia, of various degrees and in all combinations, were frequently seen. The occurrence of aplastic anemia was also noted in some cases.

The keratitis associated with the present case was most interesting because of its unusual clinical course and its relation to keratitis profunda and keratitis disciformis. In another case of atypical lichen planus with aplastic anemia, a superficial punctate keratitis was demonstrated bilaterally.

The keratitis described in this paper closely simulated keratitis profunda, with two exceptions: (1) The anterior layers of the cornea were not involved in the earlier stages, and (2) no vascularization, deep or superficial, was ever present during any stage of the ocular involvement. Occasionally, a permanent deep opacity of the cornea persists in keratitis profunda, but this sequela did not develop in the present case.

Keratitis disciformis, which the keratitis here described also resembled, begins with localized central epithelial edema of the cornea, which eventually extends to the deeper layers. This process produces a central, indolent parenchymatous infiltration, characterized by a discoid form,<sup>3</sup> which then becomes permanent. In the present case, the pathologic process began in the posterior layers of the cornea centrally and spread anteriorly, and was followed by formation of vesicles in the epithelium in an area corresponding to the deeper infiltration. The cornea finally cleared, leaving a faint Stähli-Hudson line.

The pathologic alterations observed in this case did not conform to the classic clinical course and diagnostic morphologic changes which characterize the interstitial keratitides seen with syphilis and tubercu-

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3. Berliner, M. L.: *Biomicroscopy of the Eye*, New York, Paul B. Hoeber, Inc., 1943, vol. 1, p. 519.

losis. In addition, the patient's reactions to serologic tests and to intracutaneous injections of tuberculin were negative on several occasions. That the keratitic process kept pace with the activity of the cutaneous lesions was clearly illustrated during several remissions and relapses. This parallelism strongly suggested a relationship of cause and effect between the keratitis and the atypical lichen planus.

That certain types of infectious diseases of the skin may produce secondary inflammations of individual structures within the human eyeball has been recognized from time to time in previous publications. Participation in the disease process of the uveal tract, in part or as a whole, has been frequently described in cases of erysipelas, carbuncle, pemphigus, epidermolysis bullosa, urticaria, erythema nodosum, erythema exudativum multiforme and lichen planus.

Many cases of conjunctival involvement have been recorded with such conditions as molluscum contagiosum, Boeck's sarcoid, psoriasis, erythema nodosum, summer prurigo and acanthosis nigricans. The dermatogenous cataract has been seen as a complication following neurodermatitis, scleroderma, poikiloderma atrophicum vasculare, chronic eczema and Darier's disease (keratosis follicularis).

Keratitis not frequently has been associated with the following dermatologic conditions: acne rosacea, psoriasis, erythema exudativum multiforme, dermatitis herpetiformis, epidermolysis bullosa, xeroderma pigmentosum and pityriasis rubra pilaris.

The cause of atypical lichen planus remains unknown, but two lines of reasoning are worthy of consideration. 1. All the patients had received suppressive doses of quinacrine for long periods before the cutaneous eruption manifested itself. Discontinuance of the drug invariably resulted in decided improvement of the cutaneous lesions. Evidence has thus accumulated which supports the contention that quinacrine, acting as a toxic agent, could be responsible for the picture of atypical lichen planus. 2. All the patients with this type of eruption had been in the Southwest Pacific, particularly in New Guinea and on adjacent islands. It was noted that the cutaneous lesions began to regress in almost all patients who were removed from these regions. Of equal importance, therefore, is the possibility that climatic variations, pollens, various insects or irritants might have been responsible, as in contact dermatitis.

The first line of reasoning suggests a mechanism to explain the keratitis in the case reported here. I have observed that quinacrine is excreted perilimbally, its presence being demonstrated by sclerotic scatter as a yellowish green limbal glow. Epithelial edema<sup>4</sup> and super-

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4. Chamberlain, W. P., Jr., and Boles, D. J.: Edema of Cornea Precipitated by Quinacrine, *Arch. Ophth.* 35:120-134 (Feb.) 1946.

ficial pigmentation of the cornea and bulbar conjunctiva<sup>5</sup> have been noted in other cases after long-continued administration of the dye. Since the ciliary processes secrete the dye into the anterior chamber, the cornea is constantly bathed with a solution of quinacrine. This probably sensitizes the corneal tissues and renders them more vulnerable to other toxic substances. Since the keratitis in this case made its first appearance at the height of the cutaneous disorder (four months after the first cutaneous lesion appeared), and since it was not present during the preeruptive stage, it is logical to assume that toxic products formed by the destructive cutaneous lesions settled in the quinacrine-sensitized cornea, causing the keratitis described in this case.

#### SUMMARY

1. A rare case of deep keratitis occurring in atypical lichen planus associated with alopecia areata, poliosis, vitiligo and hyperpigmentation is described.

2. It is noted that vascularization of the cornea was not observed in this keratitic lesion, which finally underwent complete regression.

3. It is further noted that penicillin and sulfadiazine in no way altered the course of the keratitis.

4. The relation of this keratitis to keratitis profunda, keratitis disciformis and parenchymatous keratitis of the syphilitic and tuberculous types are discussed.

5. Atypical lichen planus is defined, and its three types are briefly outlined.

6. It is reasoned that quinacrine ("atabrine"), in the role of a sensitizing agent to the corneal tissues, was probably responsible for the development of the keratitis, together with toxic products of the destructive cutaneous lesions.

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5. Sugar, H. S., and Waddell, W. W.: Ochronosis-Like Pigmentation Associated with Use of Atabrine (Quinacrine), Illinois M. J. **89**:234-239 (May) 1946.

## AN AID IN DETECTING TRACHOMA-LIKE INCLUSION BODIES IN THE CONJUNCTIVA

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IN 1907, while in Java to investigate the immunology of syphilis, Halberstädter and von Prowazek<sup>1</sup> discovered the inclusion bodies associated with trachoma. This observation was the first demonstration of such bodies in the eye.

A few investigators have expressed the belief that the infectious agent of trachoma is a rickettsial body.<sup>2</sup> In support of this view, Cuénod and Nataf<sup>2b</sup> claimed the passage of the agent through the louse onto a normal conjunctiva, with the production of clinical trachoma.

Halberstädter-Prowazek inclusion bodies are observed in the conjunctival scrapings in cases of certain ocular infections. Although trachoma is the most important of these, similar bodies are also seen in cases of inclusion conjunctivitis, psittacosis and lymphogranuloma venereum.<sup>3</sup> Whether, as Lindner<sup>4</sup> stated, these bodies constitute the agent causing trachoma or whether they are the by-products of a tissue reaction to this agent is not clear. What does seem to be well established is that the bodies are to be found in the early phases of the infections noted. This fact is of great importance for the early diagnosis of these conditions. Since early diagnosis offers the best prospects of satisfactory therapy, the early detection of these inclusion bodies becomes proportionately important. The purpose of this paper is to indicate a method that will aid in the laboratory diagnosis of Halberstädter-Prowazek inclusion bodies in the conjunctiva.

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1. Duke-Elder, W. S.: *Textbook of Ophthalmology*, St. Louis, C. V. Mosby Company, 1940, vol. 2, p. 1599.

2. (a) Busacca, A.: Is Trachoma a Rickettsial Disease? *Arch. Ophth.* **17**: 117 (Jan.) 1937. (b) Cuénod, A., and Nataf, R.: *Researches on the Aetiology of Trachoma*, *Brit. J. Ophth.* **21**:309, 1937; (c) Deuxième note sur la présence d'éléments infra-microbiens dans la follicules trachomateux, *Arch. d'opht.* **52**:573, 1935; (d) Sur la présence d'éléments rickettsioides très abondants et très constants dans les follicules trachomateux, *Rev. internat. du trachome* **12**:110, 1935.

3. Thygeson, P.: *Viruses and Virus Diseases of Eye*, *Arch. Ophth.* **29**:635 (April) 1943.

4. Lindner, K., in Berens, C.: *The Eye and Its Diseases*, Philadelphia, W. B. Saunders Company, 1936, p. 439.



## PRESENT INVESTIGATION

While I was stationed with the Army in the Fiji Islands, a survey on trachoma among the inhabitants was conducted. In compiling the results of that study,<sup>5</sup> I needed photomicrographs to show the conjunctival inclusion bodies of trachoma. Many photographic technics were attempted in order to find the best means of demonstrating the inclusion bodies in stained conjunctival smears. With the use of different types of photographic color filters, various optical effects were produced. By this means was discovered a most satisfactory aid in detecting trachoma-like inclusion bodies.

*Material.*—All the smears which were positive for inclusion bodies were obtained from permanent inhabitants of the Fiji Islands. This population included Melanesians, Melanesian-Caucasian hybrids and East Indians.

The smears were obtained by scraping the upper tarsal conjunctiva with a semi-sharp instrument. This material was spread thinly on a glass slide, allowed to air dry and fixed with methyl alcohol for five minutes. Dilute Giemsa stain (1:10) adjusted to a  $pH$  of 7.2 was then applied for twenty-four hours. After being washed with distilled water and dried with blotting paper, the slides were ready for microscopic study.

By oil immersion microscopy with white light the conjunctival epithelial cells were usually clearly demarcated. The cytoplasm took a pale blue stain, while the nuclei showed as a deep reddish violet. When inclusions were present, they could be seen as deep blue particles in any of their various phases of development. These bodies were most frequently observed in the cytoplasm in close propinquity to the nucleus. Many were seen as the characteristic "cape" formations described by Lindner<sup>4</sup> and others. When the microscopic picture was that just described, namely, a pale blue cell with a reddish violet nucleus containing characteristic formations of deep blue inclusions, diagnosis was indeed a simple matter. A single glance at the microscopic field gave the answer (figure).

However, this happy mosaic did not always obtain. Occasionally the cytoplasm took on a dark reddish violet hue, which tended to obscure any inclusions present. This could not be accounted for on the basis of a faulty staining technic. Other slides subjected to the same conditions stained with perfect differentiation.

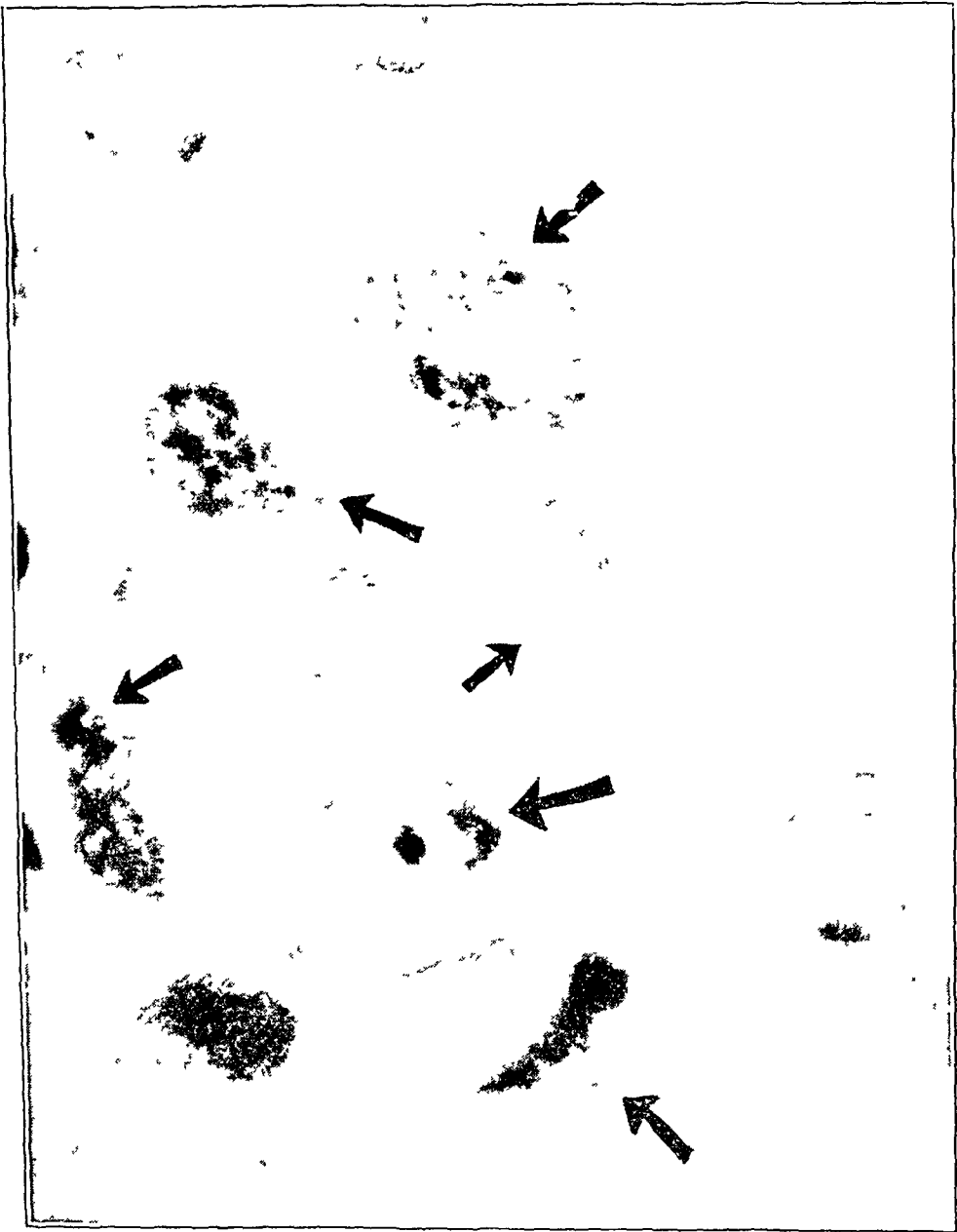
A second condition which on occasion hid the inclusion bodies was a jamming together of cells due to insufficient spreading during the making of the smear. As a result, nuclei overlay the cytoplasm of their neighboring cells. Inclusions that might be present in the cytoplasm were also covered by these nuclei. As has been noted, the reticulum of the nuclei characteristically stained a deep reddish violet. Because of its irregular meshwork and deep color, the nucleus frequently served as an excellent camouflage for any overlying or underlying inclusion bodies. Whenever possible, repeat smears were made in such instances. However, it was not always feasible to get our subjects back from their bush dwellings for this purpose. Clinic patients are often not more retrievable.

A third way in which inclusion bodies were occasionally obscured was by their occurring entirely within the nuclear contour. Fine focusing with the microscope

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5. Bodian, M.: Trachoma: A Possible Carrier State, *Arch. Ophth.* **38**:450 (Oct.) 1947.

indicated that some were within the substance of the nucleus. Others, however, seemed merely in apposition with it—either above or below. As already noted, the nucleus, with its characteristic form and color, as brought out with the Giemsa stain, is an effective camouflage for Halberstädter-Prowazek inclusions. Unless one is prepared to spend a good deal of time on each field, employing the fine adjustment, one may easily overlook an inclusion lying within a nuclear border.



Photomicrograph (1,500 magnification) of conjunctival scrapings, showing Halberstädter-Prowazek inclusion bodies in epithelial cells. Various phases and locations of the inclusion bodies may be noted (arrows). The photograph fails to show the cytoplasm of cells, but this can easily be seen in stained smears.

The aforementioned obstacles in the way of detecting inclusion bodies occurred often enough to be of significance. They were of particular hindrance during the course of a statistical survey in which hundreds of slides had to be studied. A single inclusion might be the only specific indicator on the entire slide. If this was missed, a false negative result would obtain. Those bodies which were

obscured by the means previously mentioned were particularly apt to be overlooked by ordinary microscopy.

*Method.*—By trial and error, it was found that the E, light red photographic filter (Wratten), series 23A, was the best in bringing out the inclusion bodies when stained by the Giemsa method. This filter transmits the longer wavelengths of light and absorbs the shorter ones. Thus, the red end of the spectrum passes through with little impediment. The blues and greens, however, are almost completely absorbed and hence are seen as shades of gray and black.

No appreciable variation in optical effect was discerned by placing the filter at different aspects of the microscope. The same effect was observed whether it was placed at the light source, on the substage condenser or in the ocular. Likewise, the exact material constituting the filter was relatively unimportant. Colored glass, sheet gelatin or plastic gave the same results, providing the wavelengths and color saturations were approximately the same.

One disadvantage of the red filter is that it tends to blur outlines of objects. This effect is produced by the wavelengths at the ends of the spectrum (red and blue), which tend to diminish visual acuity.<sup>6</sup> This loss of sharpness is so slight as to be of no consequence in the usual microscopic procedure. When, however, an infrequent object merited more exact study, the filter was removed so that white light could be used.

For general use, the gelatin filter was found most satisfactory. It is inexpensive, can easily be cut into desired sizes and shapes and is available in most photographic shops.

It was found more cumbersome to remove and replace filters from the substage condenser or the oculars. Hence, although the same optical effects were obtained from these locations, the most practicable method was used, namely, filtration of the light as it left its source.

In consideration of the discussion, it was found that the most convenient form of filter was a 3 inch (7.5 cm.) square of gelatin of the proper wavelength, mounted on a cardboard frame. This was placed before the substage microscopic lamp. When white light was desired for more minute structural delineation, the filter was simply removed. When the survey was resumed, the filter was as easily replaced.

*Results.*—For purposes of detecting inclusion bodies in the Giemsa-stained conjunctival smear, three structures are of particular importance: the pale blue cytoplasm of the conjunctival epithelial cell, its deep reddish violet nucleus and, not least, the deep blue inclusion body itself. When seen through the color filter previously noted, the cytoplasm becomes a pale gray, the nucleus is a medium gray and the inclusion bodies are an intense black, which stand out boldly from the surrounding field. Of course, the background is a uniform red.

Whatever structures have a red component in their stain are rendered less prominent by blending with the red background. This is especially important in the case of the nuclei, since these have a deep reddish element with the Giemsa stain, which effectively camouflages superimposed inclusion bodies in white light. With the red filter the

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6. Duke-Elder,<sup>1</sup> 1939, vol. 1, p. 938.

nuclei are seen as a medium gray reticulum. Inclusion bodies within their contours stand out sharply in black relief. A passing glance shows their presence.

When the cytoplasm occasionally stains reddish, it acts much like the nucleus in hiding inclusion bodies. The red filter uncovers them from such situations, just as in the cases of nuclear superimposition.

#### COMMENT AND CONCLUSIONS

Several months after the technics described for studying inclusion bodies had been in use I came on a similar work by Caries.<sup>7</sup> He had used almost the same filter technic to facilitate the discovery of merozoites in blood smears of malarial patients. The blue-staining ring bodies in the red blood corpuscles stood out prominently with a red light filter. Apparently, he had no occasion to search for inclusion bodies. He found the method extremely helpful in discovering malarial parasites.

It is felt that by using a red filter the study for inclusion bodies of the Halberstädter-Prowazek type is facilitated. Routine studies can be made more rapidly. Less experienced observers can pick them up with great efficiency. Even the most experienced microscopist will occasionally miss an inclusion body when its background is conducive to that end. The filter unearths these evasive stigmas.

When, as occasionally happens, these bodies are limited to the nucleus of one cell on a slide, one can see how easily that cell could be missed. Lindner stated, ". . . occasionally only one cell . . . with inclusions can be found in an entire specimen or even several smears."<sup>4</sup> That "one cell with inclusions" is of vast importance. The red filter may make it more visible.

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7. Caries, R.: Rapid Diagnosis of Malaria by the Use of a Wratten Light Filter, *J. Lab. & Clin. Med.* **28**:1150, 1943.

## OCCLUSION OF THE CILIORETINAL ARTERY

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**I**N CLOSURE of the central retinal artery, sparing of the macula with preservation of central vision due to the presence of a cilio-retinal artery is a well recognized entity. The converse, closure of the cilio-retinal artery with a normal functioning central retinal artery, has seldom been observed. Only 6 cases have been reported in the literature, and none within recent years. The main data in the reported cases are given in the accompanying table.

### *Summary of Reported Cases of Occlusion of Cilio-retinal Artery, Including Present Case \**

Author	Age, Yr.	Sex	Eye	Initial Vision	Initial Scotoma	Macula	Last Vision	Residual Scotoma
Hirsch, O.: Arch. f. Augenh. <b>33</b> : 139, 1896	31	M	R	Fingers at 4 meters	Ceco-central	Cherry red spot	6/6	Narrow band between fixation and blindspot
Zentmayer, W.: Ophth. Rec. <b>15</b> : 613, 1906	21	M	R	6/6	(No further record)			
Krauss, F.: Ophth. Rec. <b>16</b> : 196, 1907	18	F	R	5/30; eccentric	Ceco-central	Incomplete cherry red spot	5/4	Small para-central
Meller, J.: Arch. f. Ophth. <b>72</b> : 456, 1909	35	F	L	Fingers at 1 meter	Central	Cherry red spot	6/36	Small central
Levy, A.: Tr. Soc. U. Kingdom <b>29</b> : 130, 1909	22	..	R	6/60	(No further record)			
Trappe, E.: Ztschr. f. Augenh. <b>32</b> : 124, 1914	16	F	R	Fingers at 1.5 meter	Central 15-20°	Cherry red spot	5/50 eccentric	Central, 10°
Levitt .....	19	F	L	20/200	Ceco-central	Normal	20/15	Narrow band between fixation and blindspot

\* In every case there was opacity of retina extending from near the temporal margin of the optic nerve up to or including the macular zone.

Closure of the cilio-retinal artery is usually manifested by sudden loss of central vision. Young people are affected. The fundus presents a large band of retinal opacity extending from near the temporal margin of the optic nerve to or beyond the macula. A cherry red spot in the macula is a frequent finding. The margins of the optic nerve are slightly hazed, especially temporally. A cilio-retinal artery is observed coursing through the affected portion of the retina. At the beginning the probable site of occlusion may be veiled by the edema, and with

Read before the Brooklyn Ophthalmological Society, Dec. 18, 1947.

subsidence of the edema a localized narrowing in caliber of the vessel may be made out. The peripheral field of vision is normal. A large scotoma corresponds to the area of involved retina and usually includes the fixation point. With the passage of weeks, the retina slowly regains its transparency, and the fundus in general is restored to normal. The scotoma becomes gradually smaller and is finally reduced to a narrow band between the fixation point and the blindspot. In some cases a central scotoma remains permanently. There is usually no adequate etiologic factor to explain the occurrence.

In the following case the typical changes associated with closure of the cilioretinal artery were observed in the left eye. The presence, in addition, of a cilioretinal vein in the right eye represented a rare finding.

#### REPORT OF A CASE

Mrs. J. R., aged 19, was first examined on Aug. 27, 1947. She stated that on August 25 she had a general physical examination at a department store prior to employment, and that the vision of each eye was recorded as 20/20. After the examination, a job which she did not like was offered to her, and she engaged in a heated argument. Later in the same day she received a letter from her mother-in-law which greatly disturbed her. At about 8 p. m., while she was sitting in front of her home, a shadow suddenly appeared over her left eye, and faces of people walking across the street were blotted out. The visual disturbance of the left eye was unchanged at the time of her first visit.

She had measles and mumps in childhood; she had never had any operations or serious illnesses. She had been married for three years and had a healthy boy 2 years of age. At the end of April 1945 she had a miscarriage, complicated by infection, and had had leukorrhea since.

Ocular examination (August 27) revealed vision of 20/15 in the right eye and 20/200 (unimproved) in the left eye. Jaeger type 1 was read with the right eye, but no print could be read with the left eye. External examination showed nothing remarkable. The pupillary reactions were unaltered. The media of both eyes were clear. The right fundus was free of pathologic change; a typical cilioretinal artery and a cilioretinal vein were present (fig. 1 *A*). The left fundus (fig. 1 *B*) showed a large band of snow white retinal opacity with festooned borders, extending from slightly temporal to the optic nerve to the margin of the macular zone. The optic disk was round and of good color, with a round, deep physiologic cup; and the temporal, upper and lower margins were slightly hazy. The macular zone was normal, with good macular and foveal reflexes. There were two typical cilioretinal arteries, one coursing in normal retina below the involved area and the other in the middle of the edematous retina and largely obscured by it. There was a large, aberrant macular vein along the upper margin of the opaque portion of the retina, coming from the macular zone and emptying directly into the superior retinal vein in the physiologic cup. Otherwise, the central retinal artery and vein and their subdivisions were normal, and macular vessels from the superior and inferior temporal arteries and veins arched around the macular zone in the usual manner.

The peripheral field of the left eye was normal. There was an absolute central scotoma in the left eye, demonstrated in the stereoscope with Haitz charts. Tests on the Evans scotometer with a 0.6 mm. white object, using binocular fixation, revealed a large scotoma (fig. 2 *A*) which included the enlarged blindspot and extended through the fixation point 4 degrees nasally below the horizontal meridian.

On the morning of the following day (August 28) vision in the left eye and the fundus picture were unchanged. In the afternoon an intravenous injection of 100 mg. of sodium nitrite was given and an effect was immediately visible. The aberrant macular vein became fuller and clearer to view. There was an appreciable lessening of the edema of the retina. The margins of the disk became clearer.

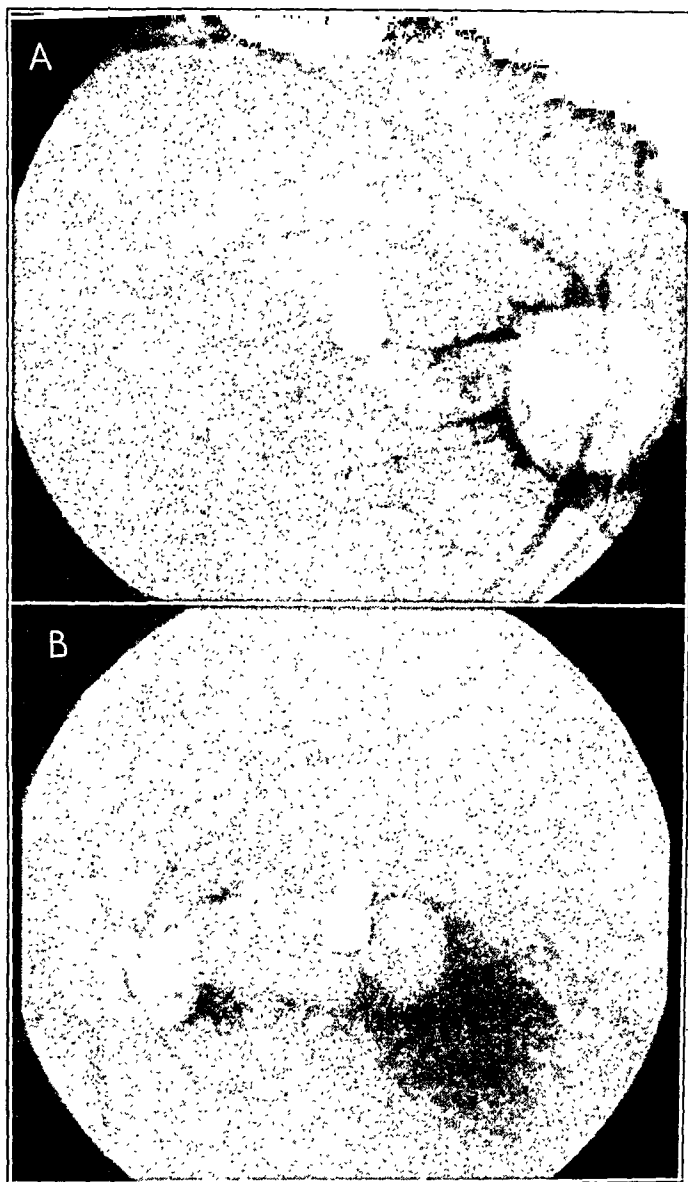


Fig. 1.—*A*, fundus of the right eye, showing cilioretinal artery and vein and an aberrant macular vein draining into the central retinal vein at the optic disk. *B*, fundus of the left eye, showing retinal edema between the optic nerve and the macula, an aberrant macular vein along the upper border of the edematous area, a cilioretinal artery within the area obscured by the edema, a second cilioretinal artery below the area and a normal macular zone.

The treatment consisted of eight daily intravenous injections of 100 mg. of sodium nitrite and the oral administration of 1 grain (0.065 Gm.) of erythrol tetranitrate and 500 mg. of nicotinic acid daily, in divided doses, for a month.

On August 29 vision in the left eye was 20/40 and the central scotoma had entirely vanished. On August 30 vision in the eye was 20/15 with Jaeger type 1 for near. On August 31, with lessening of the retinal edema, a tiny, triangular retinal hemorrhage was visible overlying the aberrant macular vein near the border of the disk, and in a week it had been entirely absorbed. The blurring of the margins of the disk disappeared entirely. The snow white retinal opacity slowly disappeared, and by September 25 the area had an almost normal appearance. The large scotoma slowly decreased in size, in correspondence with the decreasing size of the retinal lesion. A seeing area intervened between the blind-spot and the scotoma. The blindspot returned to normal. A small scotoma between the blindspot and the fixation point (fig. 2 *B*) remained as the only evidence of the vascular lesion. A narrowing in caliber of the cilioretinal artery,

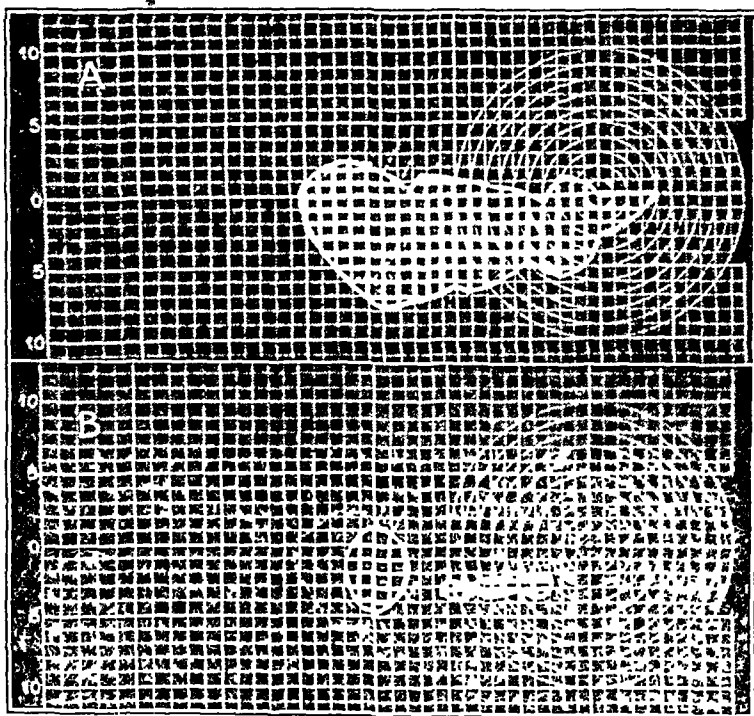


Fig. 2.—*A*, central field of vision in the eye (left) the fundus of which is pictured in figure 1 *B*. Vision was 20/200; the field was taken with a 0.6 mm. white test object on the Evans scotometer, using binocular fixation. *B*, central field of vision of the same eye taken with a 0.6 mm. white test object five weeks after onset, with fundus restored almost to normal and residual scotoma. Vision was 20/15; near vision, Jaeger type 1.

the probable site of the blockage, became evident near the margin of the disk with the lessening edema.

A complete survey for the cause was undertaken, without any significant factor being disclosed. General examination revealed nothing abnormal. The blood pressure was 120 systolic and 60 diastolic. Examination of the ears, nose and throat showed a normal condition. Gynecologic examination disclosed chronic cervicitis, with *Trichomonas vaginalis* as the infective organisms. Roentgenograms of the chest and teeth were normal. The electrocardiogram was normal. The Kolmer reaction of the blood was negative. The urine was normal. The Mantoux test gave a positive reaction to old tuberculin in 1:10,000 dilution.



## COMMENT

A quite similar clinical picture of retinal opacity may be seen in blockage of other vessels which supply the peripapillary and macular areas, such as a branch of the superior or the inferior temporal division of the central retinal artery, an aberrant macular artery coming directly from the central retinal artery or ciliary arteries other than the cilio-retinal vessel. With blockage of a ciliary vessel, no visible vascular abnormality may be evident in the fundus on ophthalmoscopic examination. Knapp<sup>1</sup> observed 2 cases with retinal edema between the disk and the macular zone without evident vascular abnormality; in both cases there was chronic cardiac disease, and he assumed that embolism of a ciliary artery near the optic nerve or, in the choroid had occurred. Goldstein and Wexler<sup>2</sup> reported a similar observation in a case of arteriosclerosis and chronic lipid nephrosis, in which microscopic examination of the eye revealed emboli in the posterior ciliary arteries on the temporal side of the optic nerve, as well as in the central retinal artery.

It is quite probable that occlusion of a cilioretinal artery may occur without the patient being aware of it, particularly when the central vision is not affected and the vision of the other eye is good.

A discussion of the exact cause of the blockage, whether embolism, thrombosis, localized vascular disease or spasm, would, as in the case of closure of the central retinal artery, be fruitless. In most of the reported cases the origin was considered embolic. Vasospasm of psychogenic origin would seem to be the most logical explanation.

## SUMMARY

The main observations in 6 cases reported in the literature and in an additional case of occlusion of the cilioretinal artery are tabulated.

The case is presented of a woman aged 19 with monocular loss of central vision; a broad band of retinal edema between the optic nerve and the macula, within which there was a localized constriction of a cilioretinal artery; a normal macular zone, and a large cecocentral scotoma. The fundus of the other eye showed a cilioretinal vein as well as a cilioretinal artery. No adequate cause of the disturbance was found on thorough investigation. Treatment consisted in intensive use of vasodilators. Almost complete recovery ensued. The fundus returned to a completely normal appearance, and only a narrow band scotoma between the blind-spot and the fixation point remained as evidence of the lesion.

991 Ocean Avenue.

1. Knapp, H.: Ueber Verstopfung der Blutgefasse des Auges: Embolie der Ciliararterien, *Arch. f. Ophth.* **14**:237, 1868.

2. Goldstein, I., and Wexler, D.: Embolism of the Central Retinal and Ciliary Arteries, in a Case of Chronic Lipoid Nephrosis with Thrombosis of the Innominate Artery, *Arch. Ophth.* **10**:70 (July) 1933.

## "SILENT" DACRYOCYSTITIS

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THE PURPOSE of this paper is to call attention to a mild type of dacryocystitis, usually mucoid in character, which is often the unsuspected cause of persistent conjunctivitis, or of unexplained tearing. This clinical entity may be called the "silent" type of dacryocystitis. For the most part, the patients comprising the present series had been treated for long periods by conventional methods, without improvement. In almost every case the lacrimal sac had been declared normal because irrigation had revealed its patency. Yet when irrigation of the lacrimal passages was performed with the purpose of collecting and examining the washings, certain clinical and bacteriologic evidence was obtained indicating inflammation of the lacrimal sac. The clinical evidence consisted in mucus, mucopus or small amounts of frank pus in the collected fluid washed through the lacrimal passages. Bacteriologically, cultures of both the conjunctiva and the material in the washings usually revealed the same pathogenic organism, *Staphylococcus aureus* A or *Staphylococcus albus* A. Most of the patients had trouble with one eye only, and irrigation of the lacrimal passages of the uninvolved eye gave washings which were entirely clear. When treatment was directed toward eradication of the dacryocystitis, generally by frequent irrigations, the conjunctivitis, which in almost every case had existed for months, subsided in a matter of weeks, recovery paralleling the clearing of the lacrimal washings. When mucopus or frankly purulent material had first been encountered, pure mucus was seen before the washings became entirely clear. Nasal examination in almost every case showed a normal condition.

Since the general tendency of late has been to underestimate the value of conservative therapy of the lacrimal tract, interest in office procedures has waned to an undeserved extent. As a consequence, many ophthalmologists perform the irrigation of the lacrimal sac in such a manner as to miss much of the information obtainable. It appears customary to have the patient sit with his head tilted back, or to have him lie on his back, when irrigation is done. If the sac is patent, the fluid enters the throat through the nasopharynx. The only fact estab-

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From the Ophthalmologic Service of Dr. Henry Minsky, the Mount Sinai Hospital.

lished is that the lacrimal passages are patent. Even the degree of patency cannot be estimated accurately; the resistance of the plunger is the only guide. In fact, even the diagnosis of patency may be incorrectly arrived at, should a nervous patient gag at the moment of irrigation. In any event, once patency is believed to be established, the sac is exonerated as normal and is forgotten. But the washings are lost, and the opportunity to study the contents is missed.

However, when the lacrimal passages are irrigated with the patient seated, head bowed, with the chin against the neck, the fluid will come out through the nose. In addition to the obvious preference on the part of the patient for a more comfortable experience, the following advantages make this technic most desirable:

1. The degree of patency can be noted by observing the rate of outflow. Thus, partial stenosis can be discovered and treated.

2. If the fluid is collected in a clean or sterile receptacle (preferably black), there may be noted the presence of fine shreds, clumps of pus or collections of mucus, indicative of inflammatory reaction in the lacrimal passages. The washings may be examined microscopically. Cultures and smears may be made. This approach is exactly that of the otolaryngologist when he suspects disease of the sinuses, especially the antrum. It is, of course, necessary to have the patient blow his nose and then to clean the inferior meatus with a moist swab before irrigation is performed, in order to be sure that nasal secretion is not mixed with the washings.

3. This method makes it possible for the ophthalmologist, in treating a stenosis or an infection, to irrigate with large quantities of fluid without causing the patient to gag or choke, and enables him better to judge the efficacy of his treatment.

The procedure of irrigation is facilitated if the ophthalmologist is also in a sitting position. The preliminary injection of cocaine and naphazoline ("privine") hydrochloride aids both in making the irrigation painless and in permitting the vasoconstriction to free those inflammatory products which might otherwise adhere to the mucosa and remain undiscovered.

The importance of examination of the washings is to be stressed especially. While many ophthalmologists irrigate in the manner suggested, they do not as a rule pay the particular attention to the character of the lacrimal washings which it deserves. Only Herman Knapp<sup>1</sup> has pointed out the full diagnostic value of irrigation of the sac, stating: . . . syringing is used: (1) for diagnostic purposes in obstructions and in inflammations: the purity of the escaping water or its admixture with other sub-

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1. Knapp, H., in Norris, W. F., and Oliver, C. A.: *System of Diseases of the Eye*, Philadelphia, J. B. Lippincott Company, 1898, vol. 3, p. 897.

stances will aid in determining the nature of the inflammation, whether catarrhal, purulent or septic.

Fuchs<sup>2</sup> stressed the value of irrigating with the patient's head forward to determine patency, but did not comment on examination of the washings themselves.

There is little likelihood of confusing the washings from the sac with nasal secretion if the nose is cleansed before irrigation. Moreover, mucus or shreds, when present, appear during the course of the washing usually only after some clear fluid has gone through. Mucus itself is generally not dislodged until the second 5 cc. of saline solution is used. To be sure that the sac is normal, therefore, at least 10 cc. of fluid must be injected. Furthermore, fluid from irrigation of the other sac is normal in each case, and, with subsequent irrigations of the involved side, the fluid becomes clearer as the condition improves. All these findings, in the absence of a pathologic condition of the nose, would substantiate the assumption that the abnormal washings come from the lacrimal passages.

#### REPORT OF CASES

Illustrative cases are described briefly.

CASE 1.—L. A., a man aged 52, first seen on May 11, 1946, had had severe catarrhal conjunctivitis in his right eye for over six months, the infection following a chalazion three months previously. He had become sensitive to penicillin and sulfonamide drugs. In addition to the conjunctivitis, examination revealed meibomitis. Externally, the lacrimal sac appeared normal. Pressure over the sac yielded no discharge. On irrigation, however, a large "icicle" of mucus appeared from the right nostril, after clear water had first come through. Cultures both of material from the conjunctiva and of the mucus revealed toxic *Staph. albus* (mannitol fermenting). Irrigation was with large quantities of benzalkonium ("zephiran") chloride and saline solution. His condition had improved so much after the first treatment that he requested irrigation when he next returned. Irrigation was therefore repeated at weekly intervals. Although two months later a slight amount of mucus still remained in the sac, the conjunctiva was entirely normal. Otolaryngologic consultation revealed no pathologic condition of the nose.

CASE 2.—R. M., a woman aged 80, seen on Oct. 18, 1946, had been treated seven months for severe follicular conjunctivitis of the right eye. The sac had been irrigated previously and declared normal. Irrigation with the patient's head forward revealed stenosis of the lacrimal passages and a "glob" of pus in the lacrimal washings. Cultures of secretions from the conjunctiva and of the pus both showed *Staph. aureus* A. Smears showed staphylococci. On irrigation with penicillin, in a concentration of 1,000 units per cubic centimeter, the pus disappeared from the washings, to be followed by a considerable amount of mucus. The conjunctiva became normal in three and one-half weeks, but a small amount of mucus was still present in the lacrimal washings.

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2. Fuchs, E.: *Text-Book of Ophthalmology*, translated by A. Duane, ed. 8, Philadelphia, J. B. Lippincott Company, 1924, p. 515.

CASE 3.—L. M., a man aged 59, first seen on June 7, 1946, had had low grade papillary conjunctivitis in the right eye for five months. The lacrimal sac had been irrigated successfully and declared normal, despite the fact that tearing was his major complaint. He had used antibiotics, with indifferent success. Irrigation revealed mucopus in the washings. Culture of material from the conjunctiva and of the pus showed a few colonies of *Staph. aureus* A. Irrigations with penicillin were instituted, and washings became clearer in a short time, along with subsidence of the conjunctivitis.

CASE 4.—M. R., a boy aged 14, first seen on Oct. 12, 1946, with a history of severe sinusitis, complained of tearing in the right eye for about six months. The conjunctiva was moderately injected. Irrigation of the lacrimal passages showed patency, but toward the end of the irrigation a considerable amount of mucus appeared. Control irrigation of the passages on the left side yielded clear fluid. Because it was felt that the associated pathologic condition of the nose was the cause of the dacryocystitis, the patient was treated by an otolaryngologist for several months. Irrigation of the lacrimal passages at that time still yielded flakes and mucus, but less than before. His tearing, having diminished considerably, hardly bothered him. In this case, the mucous dacryocystitis was probably due to an extension from the nasal cavity, and improvement occurred after treatment of the nasal sinuses.

CASE 5.—I. B., a nurse aged 43, was first seen on Jan. 24, 1947. In 1936, after bilateral conjunctivitis, an overwhelming infection of the right eye with *Staph. aureus* had occurred by direct extension, necessitating evisceration. For the four months prior to consultation she had complained of inflammation of the left eye. Examination revealed moderately severe papillary conjunctivitis with some puffiness of the margins of the lids. Cultures of material from the lid margins and conjunctiva showed nontoxic *Staph. albus* B. Irrigation of the lacrimal passages was productive of considerable mucus. Cultures of this mucus and the nasal secretion both yielded *Staph. albus* A, toxic variety. The sac was treated with irrigations of penicillin, in a concentration of 15,000 units per cubic centimeter, together with subcutaneous injections of staphylococcus toxoid and the conjunctival instillation of drops of sodium sulfacetimide and naphazoline ("privine") hydrochloride. The lacrimal washings cleared within a month, but the conjunctiva did not improve significantly until several months later. At the time of writing, the sinusitis, probably the cause of the mucous dacryocystitis, remains unchanged. She still receives nasal treatment regularly. The past history suggests a low resistance to the staphylococcus.

CASE 6.—D. B., a man aged 40, first seen on March 21, 1947, complained of tearing in both eyes for several years. The conjunctiva did not appear significantly inflamed. Irrigation of the right lacrimal passages was productive of a moderate amount of mucus; washings from the left lacrimal passages were clear, although stenosis was present. Subsequent irrigations gave clear washings from both sides, and tearing ceased in three weeks.

CASE 7.—Despite the fact that involvement of the lacrimal sac was obvious from the history alone, this rather unusual case is included because it illustrates the value of investigating the lacrimal washings in all cases of disease of the lacrimal sac. A clerk, aged 34, was seen on Nov. 20, 1945, because of severe tearing of the left eye for the previous week. The conjunctiva was normal. Only after irrigation with considerable force did a fine trickling of clear water come through. The next day, probing revealed a strong, boggy obstruction at the lower

end of the sac. When the probe was withdrawn, pus oozed through the punctum. Culture and smear of this pus showed pneumococci. A no. 3 probe was then passed to the nose, and penicillin was injected into the sac. The course of the dacryocystitis in this case may be described in four stages: (1) incomplete obstruction by an abscess-like inflammation of the mucosa; (2) drainage of the abscess, characterized by frank pus in the lacrimal washings; (3) improvement, characterized by decreasing amounts of pus and increasing amounts of mucus, and (4) resolution, characterized by the presence of mucus without pus, followed by the absence of both mucus and pus and the relief of tearing.

#### COMMENT

Dacryocystitis is generally described in the ophthalmic literature as a chronic inflammation of the lacrimal sac due to stenosis of the nasolacrimal duct, which usually is of considerable degree, if not complete. The stenosis, in its turn, develops as a result of inflammation of the nasal mucosa extending by continuity to the mucous membrane of the nasolacrimal duct. A mucopurulent or purulent discharge is present, which flows into the conjunctival sac on pressure. Sometimes a mucocele develops in cases of long-standing disease. The condition known as acute dacryocystitis is more properly designated as acute peridacryocystitis; it occurs when the organisms present in chronic dacryocystitis penetrate the submucous tissue and invade the wall of the sac itself. Thus, the "acute" inflammation is secondary to chronic dacryocystitis. These two obvious types of inflammation of the lacrimal sac appear to be the only ones generally accepted. A third type seems to deserve inclusion in the everyday thinking of the ophthalmologist.

It is not sufficiently recognized that there exists an incipient, mild, low grade dacryocystitis in which obstruction does not play an obvious role. Experience would indicate, however, that such a "silent" dacryocystitis is by no means rare, but, on the contrary, is often discovered when looked for in likely cases. If this more or less acute, although mild, dacryocystitis does not clear up, it is possible that the classic chronic type of dacryocystitis may result. It is only logical to assume that the mucous membrane of the lacrimal sac, like mucous membrane elsewhere, containing mucous cells, and sometimes mucous glands, is susceptible to mild, sometimes transient, inflammations. In cases of this type only mucus would be found. Furthermore, in the severer inflammations, in which a purulent or mucopurulent exudate occurs at first, only mucus might be noted later. The lacrimal washings in the cases reported here indicate that as the inflammation subsides mucus is always found sooner or later, before cure is complete. Thus, the presence of mucus may indicate either mild inflammation *per se* or an intermediate stage in the course of a severer dacryocystitis. Associated nasal disease may, of course, be present; it may even be the cause of the dacryocystitis. The important point is that early evidence of

dacryocystitis causing conjunctivitis, or only tearing, may be discovered and the condition adequately treated if the systematic examination of the eye includes the technic described here—qualitative and quantitative inspection of the washings resulting from irrigation of the lacrimal passages.

#### SUMMARY

A mild type of dacryocystitis, usually mucoid in character, is often the unsuspected cause of persistent conjunctivitis or of unexplained tearing. This "silent" type of dacryocystitis is overlooked if investigation of the tear passages is limited only to a determination of patency. If, however, the lacrimal washings are collected and examined both clinically and bacteriologically, the finding of mucus, mucopus or frank pus containing pathogenic bacteria will indicate the presence of "silent" dacryocystitis. In cases of this type obstruction does not play an obvious role. Once the diagnosis is established and treatment of the dacryocystitis instituted, the conjunctivitis, which in almost every case of the present series had existed for months, subsided in a matter of weeks, recovery paralleling the clearing of the lacrimal washings. Experience suggests that this low grade type of mucous dacryocystitis is not uncommon and, if not recognized, may eventually lead to more obvious inflammatory changes in the lacrimal passages.

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# THE HISTORY OF THE DARTMOUTH EYE INSTITUTE

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THE DARTMOUTH Eye Institute, of Hanover, N. H., has closed its doors. A unique institution has passed from the scene of American ophthalmology. It is worth while looking at its history.

The origin of what in 1937 became the Dartmouth Eye Institute dates back to 1919. In that year Adelbert Ames Jr. came to Hanover, N. H., to join with Prof. Charles Proctor, of the department of physics of Dartmouth College, in carrying out research on the optical properties of the human eye.

Ames is neither an ophthalmologist nor a physicist. Trained as a lawyer, he abandoned law to become an artist. Being of an analytic as well as artistic temperament, he soon became interested in the question of the relation of what one sees to what is represented on the canvas. The pursuit of this problem led to the question how the organ of sight reproduces the environment. In other words, Ames became interested in the relation of objective and subjective space.

Ames felt that to answer this broadest question he had to begin at the beginning, and he decided to investigate the problem of the image formation in the eye. This brought him to Hanover and led to the excellent studies by Ames and Proctor on the dioptrics of the eye,<sup>1</sup> and to the establishment of the Department for Research in Physiologic Optics.

The practical purpose of the study of the aberrations in the human eye was to construct an optical instrument, a camera, which would duplicate as closely as possible the image formation in the human eye. It was hoped that such an instrument would contribute further knowledge to the question of how one sees.

The help of Gordon H. Gliddon, of the lens-designing division of the Eastman Kodak Company, was enlisted in the construction of the camera.<sup>2</sup> He remained until 1936 closely associated with the research work of Mr. Ames. After that, until 1945, he was engaged in work of administrative nature at the Dartmouth Eye Institute.

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1. Ames, A., Jr., and Proctor, C. A.: Dioptrics of the Eye, *J. Optic. Soc. America* 5:22-84 (Jan.) 1921.

2. Gliddon, G. H.: An Optical Replica of the Human Eye for the Study of the Retinal Image, *Arch. Ophth.* 2:138-163 (Aug.) 1929.



It was soon found that further examination of the optical properties of the single eye would not advance materially the solution of the basic problem. Ames then began to tackle the question of binocular vision on a broad basis, leading off with one of the most complicated factors, cyclophoria, which he dealt with in an exhaustive experimental study.<sup>3</sup>

It was at this point that the work of Ames first came to the attention of ophthalmologists. More especially, Walter B. Lancaster, of Boston, became interested in the studies carried on at Dartmouth and lent his active help and advice. This became all the more important since the study of the physiology of vision necessarily brought about a consideration of anomalies of vision, the handling of clinical cases. The first fruit of measurements on persons with ocular anomalies was the construction of a device for the correction of cyclophoria in near vision. This device was published by Lancaster in a clinical report.<sup>4</sup>

Concurrently with the study of cyclophoria, Ames and Gliddon carried out an ambitious program of study of visual physiology, covering in careful measurements accommodation, astigmatism, horizontal and vertical heterophoria, and cyclophoria.<sup>5</sup> Not only were these measurements performed on a modified haploscope, uncommonly precise; the authors also discovered a number of interesting phenomena. Among them was the first indication of what was to become the most important contribution to clinical ophthalmology made by Ames and his co-workers, namely, the existence and significance of retinal asymmetries.

This particular subject was followed and studied relentlessly in the ensuing years; finally, in 1932, a series of papers were published in which the physiologic and clinical significance of the anomalies in the size and shape of the ocular images was discussed and in which the methods of measurement and of correction were presented. These papers laid the foundation for knowledge of what came to be known as aniseikonia.

It has been appreciated for a long time that a large difference in the ocular images (such as exists in the extreme cases of corrected refractive anisometropia) may present an insuperable obstacle to fusion. But it had never been considered that small relative image size differences, of the magnitude of 0.5 to 2 per cent, may create such difficulties for the fusion apparatus that the person afflicted with this condition may experience symptoms of asthenopia not accounted for by other ocular anomalies or relieved by their treatment when they are present. It was

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3. Ames, A., Jr.: Cyclophoria, *Am. J. Physiol. Optics* **7**:3-38 (Jan.) 1926.

4. Lancaster, W. B.: The Ames Spectacle Device for the Treatment of Cyclophoria with a Report of a Successful Case, *Arch. Ophth.* **57**:332-338 (April) 1928.

5. Ames, A., Jr., and Gliddon, G. H.: Ocular Measurements, *Tr. Sect. Ophth., A. M. A.*, 1928, pp. 1-68.

Ames who not only discovered this fact but studied with his co-workers the different types of possible retinal asymmetries, elucidated their physiologic and clinical significance, devised methods for their detection and measurement and for their correction and, with rare single-mindedness, insisted that aniseikonia be recognized as a clinical entity requiring measurement and correction.

But aniseikonia is not only an obstacle to fusion. Within the limits in which binocular vision is possible in the presence of an aniseikonia, it has a profound influence on spatial orientation as determined by stereopsis. This was noted at an early date by Ames and was studied thoroughly (with regard to aniseikonia in the horizontal meridian). As a means for this study, the empiric longitudinal horopter was employed. These investigations<sup>6</sup> were far more than a mere application of horopter measurements to problems of aniseikonia; they represent a significant contribution to the horopter problem in general. This is particularly true of the outgrowth of this work, the analytic treatment of the curve of the empiric longitudinal horopter by Ogle,<sup>7</sup> who had in the meantime joined the department, first as a graduate student and then as a full-fledged member.

The years following the publication of these papers were devoted to the further development of the methods of measuring and correcting aniseikonia. Patients, referred from various parts of the country, began to arrive, and the clinical end of the department was built up. It was joined by an ophthalmologist, Dr. Elmer H. Carleton, and an optometrist, Leo F. Madigan.

The more these clinical studies progressed, the more the feeling grew that aniseikonia, as a component of the sensory part of the visual apparatus, has a significant bearing on the neuromuscular anomalies of the eyes. It was at this time that Alfred Bielschowsky, of Breslau, Germany, visited this country as a lecturer. Lancaster, always maintaining his interest in the work of Ames, suggested to him that Bielschowsky might be willing to come to Hanover to join the department. Ames approached Bielschowsky, and he agreed to come for a six months' visit. During this visit he became so impressed with the possibilities which the department had to offer that he decided to return to Hanover to stay permanently.

The coming of Bielschowsky gave a tremendous impetus to the organization. The Department of Research in Physiological Optics

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6. Ames, A., Jr.; Ogle, K. N., and Gliddon, G. H.: Corresponding Retinal Points, the Horopter and Size and Shape of Ocular Images, *J. Optic. Soc. America* **22**:538-578 (Oct.); 575-632 (Nov.) 1932.

7. Ogle, K. N.: An Analytical Treatment of the Longitudinal Horopter: Its Measurement and Application to Related Phenomena, Especially to the Relative Size of the Ocular Images, *J. Optic. Soc. America* **22**:665-728 (Dec.) 1932.

was transformed into the Dartmouth Eye Institute, consisting of a research division and a clinical division. A new grant was obtained from the Rockefeller Foundation, which had in the past generously supported the work.

Bielschowsky became director of the Institute, and the staff of each division was enlarged considerably. The work of the clinical divisions, more especially, was expanded. Its medical members were granted the privileges of the staff of the Mary Hitchcock Memorial Hospital, and in the course of time the Dartmouth Eye Institute became a well regarded center of ophthalmic work in Northern New England.

As was natural with the foremost authority on ocular motility at the head of the institution, this field of ophthalmology was particularly cultivated. But there was also a close association of the clinical with the research division, and all members engaged in active research, prevalently concerned with the physiology and pathology of binocular vision and with the physiopathologic basis of the neuromuscular anomalies of the eyes. The research division continued to carry on its problems: Ames became more and more interested in the problems regarding aniseikonia and spatial orientation and its influence on the functioning of the organism; Ogle worked on refinement of the means of measuring and correcting aniseikonia and on what became known as the "induced" size effect.

In addition to all this work, the members, under the active leadership of Bielschowsky, attended numerous meetings, both ophthalmologic and optometric, gave papers and lectures and, more especially, had regular monthly gatherings at the Institute, which were well attended by ophthalmologists from New Hampshire, as well as the neighboring states, and which represented a sort of continuous informal postgraduate course in ophthalmology.

The sudden, and most untimely, death of Bielschowsky in January 1940 was a severe blow to all these activities. He was not immediately replaced by a successor, and the writer of this note attempted to carry on the responsibilities of the clinical division on an informal basis, a rather difficult task, in view of the lack of official authority to do so.

To the great relief and joy of all members of the staff, Walter B. Lancaster agreed in the fall of 1940 to head up the Dartmouth Eye Institute. He had for the preceding twenty years shown the greatest interest in its work; he had at all times actively assisted in the work with his advice; he had many times in meetings of various ophthalmologic groups placed his great authority behind the work of Ames, in the face of severe criticism of that work. It was felt by the staff that his knowledge of the field, his intimate acquaintance with the organization and traditions of American ophthalmology, the weight of his word with those best qualified in the field and, last but not least, his

inspiring personality not only would give a new and better standing to the Dartmouth Eye Institute in the medical world but also would bring its work to a new flowering under his leadership.

Unfortunately, this was not to be so. Lancaster had tacitly understood that he was to be the director of the Institute and that he would, as such, have a decisive influence on its policies. But when he came, he found that a reorganization had taken place. The director was now a layman, originally appointed by the president of Dartmouth College to raise funds for the Dartmouth Eye Institute and improve its administration, which had been run in a somewhat amateurish fashion. The policies were to be determined by a board of trustees, on which the medical members of the Institute had no influence. Lancaster himself was given the title of chief of staff. Not one to be deterred by the matter of a title, Lancaster, in spite of this disappointment, nevertheless went to work with amazing energy, trying to put his ideas to work. But he soon found that this was by no means easy. In the general policies of the Institute his word had little weight; he could do little to influence the direction of the research work, and even in the running of the clinical division he was often thwarted. It was especially painful to him that his cherished plan of developing the Dartmouth Eye Institute as a teaching institution—for which it was eminently suited—was absolutely declined. Lancaster worked and fought hard for what he had come to achieve at a considerable personal sacrifice. But, finally, he drew the only possible conclusion consistent with his dignity. In November 1942 he resigned and returned to his practice in Boston.

To every clear-sighted member of the staff it was obvious that it was the end of the Dartmouth Eye Institute when Lancaster was permitted to leave. Yet it seemed that this institution should not be left to disintegrate if it was at all possible. I was one who hoped against hope that it might be saved. I stayed on in the capacity of ophthalmologist in chief until July 1945, but it was a losing fight. Too many divergent interests prevented integrated progress. One after another, the members of the staff resigned. Various attempts at reorganization were unsuccessful; finally, in an announcement dated May 10, 1947, the closing of the Dartmouth Eye Institute was officially announced.

In spite of all the difficulties, the work continued through the years at the Institute. Its chief scope remained the field of binocular vision, aniseikonia and neuromuscular anomalies, although individual members contributed work outside these fields. The coming of Lancaster to the Institute brought renewed interest in refraction and some surgical technics, which found expression in papers published on these subjects.

Ames himself turned more and more to problems of a broader scope. He asked himself what significance the normal and abnormal, monocular

and binocular reactions have for the organism as a whole, and how they affect the functioning of the organism in space. From this he moved on to generalizations about the nature and origin of sensations and came to the conclusion that "the processes which underlie our perception of our immediate external world and those that underlie our perception of social relationships are fundamentally the same" and that "the insights gained in the study of visual sensation can serve as indispensable leads to better understanding and more effective handling of the complexities of social relationships."<sup>8</sup> Ames's investigations along these lines have as yet not appeared in print.

Every one who came in close contact with the Dartmouth Eye Institute was much impressed by the quality of the research and clinical work done there, but even more by the loyalty of the patients and the devotion to the Institute of the members of the staff. It is only just that one should ask, "Why did it have to close; why did it not last?"

As usual, the causes were multiple. The most important ones, as they appear to me, shall be mentioned.

The roots of the trouble go back very far. When aniseikonia was first presented to ophthalmologists, serious objections were raised by the leaders of the medical profession. These were never properly answered. Instead, exaggerated claims for aniseikonia were made which could not be substantiated. The cool reception by the members of the profession led, in turn, to an exaggerated sensitivity toward criticism, and an approach to less critical laymen was made in person or through the press which could not be approved by the members of the medical profession, either within or outside the Institute.

Except for a brief period during Bielschowsky's lifetime, no medical man within the staff had a significant influence on the policies or the running of the Institute. On the part of the research division, there was always expressed the fear that if such influence were established research might be made the handmaiden of the clinic, a fear which was totally unjustified. The potentialities of the Dartmouth Eye Institute as a center for research in physiology of vision, as an ophthalmic center for clinical work and clinical research and as a center for teaching were enormous. But every attempt on the part of medical members of the staff to realize these potentialities remained fruitless. They were always told that what they attempted to do was not what the Institute was for. Its only purpose was said to be to implement the work of Ames.

Ames, however, had actually lost his interest in the active work of the Institute, especially its clinical division. To him, the experimental

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8. Ames, A., Jr.: *Sensations, Their Nature and Origin: Brief Statement of the Findings of the Dartmouth Eye Institute*, Hanover, N. H., Dartmouth Eye Institute, 1945.

work in physiologic optics had long since become a means for much broader purposes. He has always been imbued with that fine humanitarian spirit that has forever pervaded the best minds of New England. Essentially never a "scientist" in the academic sense of the word, he became increasingly impatient of the plodding and painstaking work in the laboratory and totally disinterested in the strictly ophthalmologic aspects of the work of the Institute. He turned increasingly to the philosophic and social implications of the work, as he saw it. Members of both the research and the clinical division regretted this exclusive preoccupation. Those who knew of the fabulous abilities of Ames as an experimenter, of his brilliant ideas in the field of visual physiology, could not help regretting that he had so largely abandoned this work as too narrow in scope. If they expressed their regret, they were rebuked for lacking breadth of vision. Thus the tension grew, and it became increasingly evident that the future which some members of the staff had envisaged for the Institute would never materialize. Reluctantly, one by one drew this conclusion.

So the Dartmouth Eye Institute ended. To those who were closely associated with it, and who had hoped for a brilliant future for it, this is a saddening end. But even to those who are only superficially acquainted with its work, it is evident that its closing is a great loss to scientific ophthalmology. The places are all too few in which the physiology of vision is competently cultivated. In the short span of its existence, the Dartmouth Eye Institute has made lasting contributions to this field. Its closing has nipped in the bud a great many promises.

A complete bibliography of the papers published by the members of the Dartmouth Eye Institute is appended.

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# DI-ISOPROPYL FLUOROPHOSPHATE (DFP) IN TREATMENT OF GLAUCOMA

## Further Observations

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PHILADELPHIA

**D**I-ISOPROPYL fluorophosphate (DFP) has been shown to have a marked and prolonged miotic effect in normal<sup>1</sup> and in glaucomatous eyes.<sup>1b</sup> It has been shown to lower intraocular tension in these eyes. Furthermore, there is evidence that these effects are brought about entirely by inactivation of cholinesterase, and not by direct action on the iris and ciliary muscle.<sup>2</sup> Although in this respect the pharmacologic effects of DFP resemble those of physostigmine and neostigmine, the DFP-cholinesterase combination is an irreversible one.<sup>3</sup> None of the methods successfully employed to split physostigmine and cholinesterase will break down this combination. Because of these properties of DFP and, more especially, because of the prolonged effect of very dilute preparations when locally applied to the normal eye, this drug was tested for its efficacy in the therapy of glaucoma.<sup>1b</sup>

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The DFP used for these experiments was supplied by Merck & Co., Inc., Rahway, N. J.

From the Department of Ophthalmology, Hospital of the University of Pennsylvania, and Wills Hospital.

Read before the Section on Ophthalmology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

1. (a) Scholz, R., and Wallen, L. J.: The Effect of Di-Isopropyl Fluorophosphate on Normal Human Eyes, *J. Pharmacol. & Exper. Therap.* **88**:238, 1946. (b) Leopold, I. H., and Comroe, J. H., Jr.: Use of Di-Isopropyl Fluorophosphate in Treatment of Glaucoma, *Arch. Ophth.* **36**:1 (July) 1946.

2. (a) Leopold, I. H., and Comroe, J. H., Jr.: Effect of Di-Isopropyl Fluorophosphate on the Normal Eye, *Arch. Ophth.* **36**:17 (July) 1946. (b) Comroe, J. H., Jr.; Todd, J., and Koelle, G. B.: The Pharmacology of Di-Isopropyl Fluorophosphate in Man, *J. Pharmacol. & Exper. Therap.* **87**:281, 1946.

3. (a) Koelle, G. B., and Gilman, A.: The Relationship Between Cholinesterase Inhibition and the Pharmacological Action of Di-Isopropyl Fluorophosphate, *J. Pharmacol. & Exper. Therap.* **87**:421, 1946. (b) Gilman, A., and Cattell, M.: Systemic Agents: Action and Treatment, in Andrus, E. C., and others: *Advances in Military Medicine*, Boston, Little, Brown & Company, 1948, vol. 2, chap. 36, p. 561.

The initial studies indicated that DFP in 0.05 and 0.1 per cent concentrations in peanut oil could successfully lower intraocular tension in glaucomatous eyes and that its length of action was greater than that of previously employed miotics. In addition, these early studies suggested that DFP might be effective in some glaucomatous eyes when other miotics in the usually recommended concentrations had failed. Subsequent favorable reports on the use of DFP have been made by McDonald,<sup>4</sup> Lebensohn,<sup>5</sup> Haas,<sup>6</sup> Dunphy<sup>7</sup> and von Sallmann.<sup>8</sup> The least favorable results were those of Marr,<sup>9</sup> who found that only 1 of every 6 glaucomatous eyes in which the disease could not be controlled by other miotics could be held in normal tension by DFP for four months or longer. Dunphy<sup>7</sup> reported that DFP was successful in approximately 1 of every 3 eyes with chronic glaucoma that had failed to respond to other miotics. These studies were all on small series of patients who were observed for six months to one year. Therefore, it seemed advisable to determine the efficacy of DFP when observed in a large group for a longer period.

#### METHOD

Three hundred and seventy eyes of 252 patients with glaucoma in one or both eyes were tested with DFP during a period of thirty-seven months. In almost every case other miotic agents were tried before DFP was used. Tensions were estimated with a Schiøtz tonometer, tetracaine hydrochloride U. S. P. (0.5 per cent) being used for topical anesthesia. Visual acuities and visual fields were checked at regular intervals. All eyes were examined with a gonioscopic lens, and attempts were made to classify them on the basis of a wide or a narrow angle. Only in eyes in which the tension was maintained at or below 30 mm. of mercury and in which no loss of visual fields occurred for a period greater than four months was the glaucoma considered controlled.

DFP was diluted in peanut oil and in liquid petrolatum U. S. P. The concentrations employed were 0.01, 0.025, 0.05 and 0.1 per cent. Other miotics employed were physostigmine, both the salicylate and the sulfate, in 0.25 to 1 per cent concentration; pilocarpine nitrate, in 1 to 6 per cent concentration; combinations of pilocarpine and physostigmine; neostigmine hydrobromide, 5 per cent, with methacholine chloride U. S. P. (mecholyl chloride<sup>B</sup>), 20 per cent, and furfuryl

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4. McDonald, P. R.: The Treatment of Glaucoma with Di-Isopropyl Fluorophosphate, *Am. J. Ophth.* **29**:1071, 1946.

5. Lebensohn, J. E.: Di-Isopropyl Fluorophosphate ("DFP") in Treatment of Glaucoma, Correspondence, *Arch. Ophth.* **36**:621 (Nov.) 1946.

6. Haas, J. S.: Response to DFP, *Am. J. Ophth.* **31**:227, 1948.

7. Dunphy, E.: Observations on the Use of Miotics, read before Section on Ophthalmology, College of Physicians, Philadelphia, March 1948.

8. von Sallmann, L.: Medical Treatment in Ophthalmology, Panel Discussion, New York Society of Clinical Ophthalmology, New York, April 1948.

9. Marr, W. G.: Clinical Use of DFP in Chronic Glaucoma, *Am. J. Ophth.* **30**:1423, 1947.

trimethylammonium iodide (furmethide<sup>11</sup>), 10 per cent. In over 300 eyes more than one miotic other than DFP was tried; as many as five different miotics were tried in some eyes.

### RESULTS

The results are summarized in table 1. In 116 of the 263 eyes with the chronic type of glaucoma, no miotic tried lowered the tension below 30 mm. of mercury for a four month period. Of the remaining 147 eyes, 77 were benefited by other miotics and DFP. In 70 eyes DFP successfully lowered the tension for at least four months after other miotics had failed; that is, in 26 per cent of all the eyes (1 of every 4 eyes) with chronic simple glaucoma in which the disease was not controlled by other miotics, it was controlled by DFP. The results in cases of narrow angle glaucoma were better than those in cases of the wide angle type.

TABLE 1.—*Comparison of Results of Treatment of Eyes with Various Types of Glaucoma by Means of DFP and Other Miotics*

Type of Glaucoma	Number of Eyes	Eyes Benefited by Other Miotics *	Eyes Benefited by DFP
Chronic glaucoma			
Wide angle.....	235	74	127
Narrow angle.....	28	3	20
Acute glaucoma.....	14	2	8
Secondary glaucoma			
Aphakia.....	53	8	39
Uveitis.....	18	2	11
Thrombosis of central retinal vein....	6	0	0
Exfoliating lens capsule.....	1	0	1
Buphthalmos.....	4	0	2
Absolute glaucoma.....	7	0	0
Juvenile glaucoma.....	2	0	0
Intraocular growth.....	2	0	0
Total.....	370	89	208
Per cent of eyes controlled.....		24.05	53.5

\* Tension 30 mm. of mercury or below (Schlötz).

Of the eyes with acute glaucoma, DFP was successful in lowering the tension below 30 mm. of mercury in 42 per cent in which the disease was not controlled by other miotics. Of the eyes with aphakic glaucoma, DFP lowered the tension below 30 mm. of mercury in 31 (58.4 per cent) of the eyes in which it was not reduced by other miotics. In 50 per cent of the eyes with glaucoma secondary to uveitis, DFP lowered the tension satisfactorily where other miotics had failed. DFP was not successful in cases of absolute glaucoma or of glaucoma secondary to venous thrombosis or intraocular growth. It failed in 2 eyes with juvenile glaucoma. It maintained an acceptable tension for four months in 1 eye with an exfoliating capsule of the lens and in 2 eyes with

buphthalmos. Of the total 370 eyes, 24 per cent were benefited by other miotics and 53 per cent by DFP. When the 89 eyes benefited by other miotics were excluded, DFP was found to have been successful in 119, or 42 per cent, of the remaining 281 eyes.

In table 2 is indicated the length of time that DFP maintained the tension and visual fields in 189 eyes with chronic glaucoma, buphthalmos and exfoliating lens capsule. Only those eyes in which the tension was controlled for four months or longer were listed as benefited in table 1. In 83 eyes the disease has been controlled over one year; in 33, over two years, and in 5, three years. In 38 of these eyes resistance to the

TABLE 2.—*Duration of Therapy*

Number of Months	Number of Eyes Controlled by DFP
Less than 3 *	70
4-6.....	53
6-12.....	53
12-18.....	28
18-24.....	22
24-30.....	28
30-36.....	1
36+.....	4

\* Eyes in which glaucoma was controlled for less than three months are not considered as controlled in table 1.

TABLE 3.—*Comparison of Effect of Miotics on Glaucomatous Eyes in Which Surgical Measures Against Glaucoma Had Failed*

Number of Surgically Treated Eyes	Number of Previous Unsuccessful Operations for Glaucoma	Eyes Benefited by DFP	Eyes Benefited by Previous Miotic
88	1	38	19
13	2	7	3
12	3	3	0
5	4	3	1
<u>118</u>		<u>51</u>	<u>23</u>

tension-lowering properties of DFP developed at varying times during the first year. The miotic properties, however, were not noticeably effected.

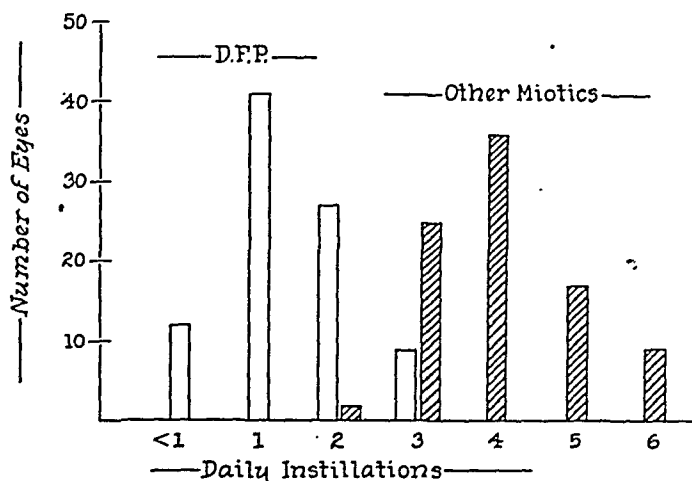
In table 3 are compared the effects of miotics on glaucomatous eyes in which surgical treatment had failed. Of 88 eyes in which one operation for glaucoma had been unsuccessful, 19, or 21 per cent, were controlled by other miotics and 43 per cent were controlled by DFP; of the 30 eyes operated on unsuccessfully two, three or four times, only 4 responded to other miotics, whereas 13 were controlled by DFP.

In the chart are compared the frequency of instillation of DFP and that of other miotics required to control the intraocular tension



in glaucomatous eyes in which it was successfully controlled by other miotics as well as DFP. It is evident that notably fewer instillations of DFP were required.

Table 4 lists the miotics which were unsuccessful in controlling tension in the eyes in which D F P was effective. It is evident that D F P



Comparison of the number of instillations of D F P and of other miotics required to control the intraocular tension in the same (89) eyes.

TABLE 4.—*Miotics Unsuccessfully Employed in Glaucomatous Eyes Controlled by D F P*

Miotic Unsuccessfully Used	Type of Glaucoma		
	Chronic Glaucoma	Aphakic Glaucoma, No. of Eyes	Acute Glaucoma, No. of Eyes
Pilocarpine nitrate, 1%.....	4	..	..
Pilocarpine nitrate, 3%.....	5	5	..
Pilocarpine nitrate, 6%.....	8	..	3
Pilocarpine nitrate, 1%, and physostigmine salicylate, 0.25%.....	14	..	..
Pilocarpine nitrate, 1%, and physostigmine salicylate, 0.5%.....	12	10	..
Pilocarpine nitrate, 2%, and physostigmine salicylate, 0.5%.....	8	8	..
Pilocarpine nitrate, 2%, and physostigmine salicylate, 1%.....	2	..	..
Physostigmine salicylate, 1%.....	5	4	1
Neostigmine hydrobromide, 5%, plus methacholine chloride, 20%.....	13	8	6
"Furmethide" hydrobromide, 10%.....	10	4	3

was able to lower tension for at least four months in eyes not controlled by 1 to 6 per cent pilocarpine nitrate, 1 to 2 per cent pilocarpine nitrate with 0.25 to 0.5 per cent physostigmine salicylate or sulfate, 5 per cent neostigmine hydrobromide with 20 per cent methacholine chloride, or 10 per cent furmethide.<sup>11</sup>

Table 5 reveals the concentrations of DFP employed in the eyes controlled by the drug. Although a few eyes responded to concentrations as low as 0.01 per cent, the majority required a concentration of 0.05 or 0.1 per cent.

In this series, 14 eyes in which the tension was not controlled by any previous miotic were treated with DFP, with interesting results. In every case the tension was lowered with DFP, though in 4 cases the medication was discontinued within three months, so that the disease in these eyes was considered uncontrolled. In the others, DFP was used with successful results from four to twelve months, but was then discontinued. The interesting feature is that in all these eyes the tension was subsequently controlled by other miotics or became normal with no miotic at all. In 1 eye the tension was controlled by 10 per cent furmethide<sup>R</sup> used six times a day; in 3, by 3 per cent pilocarpine nitrate used five times a day; in 4 by 0.5 per cent physostigmine

TABLE 5.—*Concentration of DFP Solution in Peanut Oil Employed in Control of Intraocular Tension*

Concentration in Peanut Oil, per Cent	Number of Eyes Controlled
0.01	4
0.02	15
0.05	86
0.1	103

salicylate or sulfate and 1 per cent pilocarpine nitrate, used four times a day, and in 4, with no miotic at all. In the last group, 3 of the 4 eyes had aphakic glaucoma, though there was no question that the patients had glaucoma, since they had been treated for some time prior to the institution of DFP therapy. One explanation of this may be that DFP, through its strong miotic effect, may have broken some peripheral anterior synechias and thus cleared part of the angle. It is also possible that in the cases of aphakic glaucoma a low grade uveitis subsided, with accompanying improvement in intraocular tension, so that miotics were no longer required.

When liquid petrolatum and peanut oil as vehicles were compared in the same eyes, better results were always obtained with the peanut oil preparations. DFP was poorly soluble in liquid petrolatum and frequently came out of solution. Dilutions of DFP were stored for fourteen months at room temperature and then compared clinically with freshly made solutions of the drug. The solutions were used in 20 eyes with chronic glaucoma; in every instance the aged dilutions were as effective in lowering and maintaining the tension as the fresh solutions.

DFP in peanut oil has been shown to be capable of storage for one year at room temperature without loss of anticholinesterase activity and to withstand autoclaving at 117 C.<sup>8a</sup>

#### COMMENT

From this study, and from previous ones, there is no doubt that DFP lowers intraocular tension in glaucomatous eyes. It is further evident that DFP has a longer duration of action than any miotic previously employed and that it will control the intraocular tension in some eyes in which other miotics are not effective. DFP also lowers the intraocular pressure in some eyes in which the glaucoma has not been controlled by surgical procedures.

Although, for these reasons, DFP is a valuable addition to the medical armamentarium against glaucoma, the drug does not fulfil all the requirements of an ideal antiglaucomatous miotic agent. It has several disadvantages. It frequently produces ciliary spasm, which has such undesirable effects as blurring, headache and brow ache. On rare occasions, an increase in tension may result from its use. This occurred in 6 eyes of the present series. This effect may be due to narrowing of the angle by an engorged ciliary body. DFP has been shown to dilate the ocular vessels and to increase the permeability of the smaller ones.<sup>10</sup> The increase in permeability may produce engorgement of the ciliary body and increase the protein content of the aqueous sufficiently to embarrass the angle. This mechanism should result in an increased intraocular tension more frequently in eyes with narrow angles than in those with wide angles. One cannot draw any definite conclusion from the results in 6 eyes. However, in 4 eyes gonioscopic examination showed narrow angles, whereas the other 2 eyes had wide angles, free of synechias. Haas<sup>6</sup> and Dunphy<sup>7</sup> suggested that eyes of the narrow angle type may be more prone to this increase in intraocular tension. It may be that the use of a vasoconstrictor agent, as suggested by the clinical studies of Sugar,<sup>11</sup> or of an antihistamine drug, as tried experimentally by von Sallmann,<sup>10c</sup> would prevent this rise in tension. The present data are insufficient to explain why, on rare occasions, an eye with narrow angle glaucoma showed a rise in tension, whereas in many other eyes with narrow angles the tension was controlled.

Ten eyes of 6 patients acquired sensitivity to DFP in peanut oil. In 4 patients this was shown to be a sensitivity to peanut oil, and in

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10. (a) Leopold and Comroe.<sup>1b</sup> (b) Scholz, R.: Studies on the Ocular Reactions of Rabbits to Di-Isopropyl Fluorophosphate, *J. Pharmacol. & Exper. Therap.* 88:23, 1946. (c) von Sallmann, L., and Dillon, B.: Effect of DFP on Rabbit Eyes, *Am. J. Ophth.* 30:1244, 1947. (d) Aldrege, W. H.; Davson, H.; Dunphy, E. B., and Uhde, G. I.: Effect of DFP Vapor on the Eye, *ibid.* 30:1405, 1947.

11. Sugar, S. H.: Acute Glaucoma, *Am. J. Ophth.* 30:451, 1947.

2 patients, to DFP itself. Cessation of therapy resulted in rapid clearing of the local dermatitis. Preparations in liquid petrolatum may be used safely in some eyes sensitive to peanut oil.

Marr<sup>9</sup> reported a case of retinal detachment in a patient with high myopia following the use of DFP. No retinal detachment occurred in this series of 370 eyes, but we learned of a case in which the detached retina may have been due to DFP.<sup>12</sup> Macrae<sup>12</sup> saw a man aged 40 with a fairly high degree of myopia and chronic simple glaucoma in whom retinal detachment developed while he was under treatment with a 0.2 per cent solution of DFP. The retinal detachment was first noticed sixteen days after the beginning of daily DFP therapy. It is possible that ciliary spasm might result in retinal detachment, particularly in eyes with degeneration of the peripheral retina or marked retinal thinning. Gradle and Snydacker<sup>13</sup> reported 3 cases of retinal detachment following the use of pilocarpine and physostigmine in 447 glaucomatous eyes. Retinal detachment, therefore, occurs in glaucomatous eyes under treatment with other miotics.

Certain recommendations for the use of DFP may be made from this study. One should be fully aware of its many disadvantages before employing the drug. It is effective in cases of mild, early chronic simple glaucoma in concentrations as low as 0.01 per cent, but best results are obtained with concentrations of 0.025 to 0.1 per cent in peanut oil. The weaker the concentration successfully employed, the fewer the undesirable symptoms.

The drug will be helpful in some eyes with chronic simple glaucoma not controlled by other miotics, and it can also be employed safely in eyes which respond to other miotics. Fewer instillations of DFP will be required than of other miotics, and the diurnal fluctuations in tension will be reduced because of the greater length of action of DFP.

In cases of aphakic glaucoma, DFP appears to be the drug of choice, provided the glaucoma is not due to the vitreous block, described by Chandler and Johnson.<sup>14</sup> It is interesting to note how few aphakic patients are troubled by ciliary spasm. An occasional aphakic eye on which an extracapsular extraction had been performed had some symptoms. This observation suggested that firm insertion of zonular fibers must be present for the pain of ciliary spasm to develop.<sup>1b</sup> Dunphy<sup>7</sup> also noted this absence of symptoms in aphakic eyes and suggested

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12. Macrae, H. M.: Personal communication to the authors.

13. Gradle, H. S., and Snydacker, D.; Retinal Detachment Occurring in Primary Compensated Glaucoma, *Am. J. Ophth.* **23**:52, 1940.

14. Chandler, P. A., and Johnson, C. C.: A Neglected Cause of Secondary Glaucoma in Eyes in Which the Lens Is Absent or Subluxated, *Arch. Ophth.* **37**:740 (June) 1947.

that it was due to the high cholinesterase content of the exposed vitreous body.

DFP can be used successfully in eyes with acute glaucoma in 0.05, 0.1 or 0.2 per cent concentration.

It is necessary to call attention to the strange relation of DFP and physostigmine. If physostigmine is instilled into a normal eye of a subject and fifteen minutes later, when the miosis has occurred, DFP is instilled in both eyes, the two pupils do not remain constricted for the same length of time. The eye that received DFP alone remains constricted for ten to fourteen days, whereas the eye that received both physostigmine and DFP returns to the preinstillation size in two to three days. In other words, physostigmine prevents the action of DFP. Physostigmine has protected the cholinesterase from the DFP.<sup>15</sup> *This phenomenon has been demonstrated also in cats, in which a small dose of physostigmine protects against a subsequent large fatal dose of DFP.*<sup>3b</sup> When the order of injection is reversed, the animals exhibit an increased and long-lasting sensitivity to physostigmine. These studies suggest that best results will be obtained with DFP when it has not been preceded by physostigmine or neostigmine, for these drugs will block the action of DFP against cholinesterase. However, if DFP is used first and physostigmine subsequently, the anticholinesterase effect will be enhanced. In other words, DFP should be used prior to physostigmine, and not in the reverse order.

#### SUMMARY

Di-isopropyl fluorophosphate (DFP) successfully lowered intraocular tension in 208 of 380 glaucomatous eyes.

DFP was effective in concentrations ranging from 0.01 to 0.1 per cent. The majority of eyes were controlled by a 0.05 to 0.1 per cent concentration of DFP in peanut oil.

Preparations of DFP in peanut oil were more effective than similar concentrations in liquid petrolatum U.S.P.

DFP lowered intraocular tension successfully in eyes with chronic glaucoma, acute glaucoma, buphthalmos, aphakic glaucoma and glaucoma secondary to uveitis and exfoliating lens capsule, although other miotics had previously failed. The best results were seen in eyes with aphakic glaucoma.

Decidedly fewer instillations of DFP were required to maintain a satisfactory intraocular tension in eyes in which the tension was also controlled by other miotics.

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15. Comroe, J. H., Jr.; Todd, J.; Leopold, I. H.; Koelle, G. B.; Bodansky, O., and Gilman, A.: The Effect of Di-Isopropyl Fluorophosphate (DFP) upon Patients with Myasthenia Gravis, *Am. J. M. Sc.* **212**:641, 1946.

A fourteen month old solution of DFP in peanut oil showed no loss of potency.

DFP has several disadvantages when used as an antiglaucomatous miotic. It produces ciliary spasm, with associated brow ache, headache, eye ache and visual blurring. In 6 eyes in this series a rise in intra-ocular tension followed its local instillation. Local sensitivity may result from it or its solvent. Some patients acquire a resistance to its tension-lowering property after several months of treatment. Retinal detachments have been reported to follow its use in patients with high myopia.

Its action is inhibited by the previous use of physostigmine.

1930 Chestnut Street.

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#### ABSTRACT OF DISCUSSION

DR. LEO L. MAYER, St. Louis: One of the difficulties Dr. Leopold mentions is the painful ciliary spasm. This can be overcome by using the lower concentration on the first administration of the drug. Then, gradually, the concentration of the drug can be increased as is seen fit; when the control period of the tension is below 30 mm. and no changes in the field occur, that concentration may be used thereafter.

With another type, absolute glaucoma, my experience has differed from the authors.<sup>1</sup> In the cases of absolute glaucomas which I have had to deal with, the principal reason for use of the miotic, and of DFP, was the intense pain. I admit that even when I used DFP the tension did not come down to normal, but in over 30 cases in which absolute glaucoma was present in one eye or in both eyes the patient was much more comfortable when the DFP was used than with other miotics, such as pilocarpine and physostigmine, and there was no pain whatever. I urge you to use DFP after operation for absolute glaucoma. Perhaps the patient has chosen not to have an operation; vision is gone, but he still complains of pain. With such patients, I feel, DFP has an additional use in relieving the pain, although it does not reduce the tension.

WILLIAM F. HUGHES JR., Chicago: Dr. Leopold and Dr. McDonald have done a valuable service in presenting this follow-up study of their large series of patients with glaucoma treated with DFP. This confirmatory evidence of their previous study affords some reassurance to those of us who are occasionally disconcerted by the unfavorable responses of some patients. Their most striking results with DFP after other miotics had failed were obtained in the treatment of chronic narrow angle glaucoma, of secondary glaucoma complicating aphakia and following uveitis.

In order to compare the results obtained in the glaucoma clinic of the Illinois Eye and Ear Infirmary with those of Leopold and McDonald, the cases previously discussed in a preliminary report by Dr. Joseph Haas<sup>2</sup> before the Chicago Ophthalmological Society in December 1946, and several additional cases, are reviewed. The data have been classified in a manner identical with that used by Leopold and McDonald. A total of 40 eyes were given sufficient trial with DFP that its efficacy

could be determined. The tension of only 2 eyes had previously been controlled by other miotics, usually carbachol U.S.P. (carbamylcholine chloride) or, less frequently, a combination of pilocarpine and physostigmine. The average visual field efficiency was 25 degrees. The majority of the patients received 0.05 per cent DFP in peanut oil, usually as often as two or three times a day, if necessary, before its use was discontinued. In a few patients, the strength was increased to 0.1 per cent, without additional benefit. Of 18 eyes with chronic wide angle glaucoma, only 1 maintained normal tension and visual fields for four months under treatment with DFP. This patient had had one previous unsuccessful filtering operation and had received carbachol U.S.P., in addition to DFP. For 2 eyes in which the tension was previously controlled with carbachol the treatment was changed to DFP, and the tension remained normal for only three months. Of 4 eyes with chronic narrow angle glaucoma, 1 was controlled with DFP for four months. Of 10 aphakic eyes with glaucoma, 2 eyes (of the same patient) were controlled for twenty months with DFP. The drug failed to control the tension in 4 eyes with exfoliation of the lens capsule (open angle type), in 2 eyes with absolute glaucoma and in 2 eyes with juvenile glaucoma. In 17 of the eyes described previously, DFP did not produce any reduction of tension, even temporarily.

It is difficult to determine the reason for the discouraging results obtained in this small series of cases, in which only 1 of 13 eyes responded to DFP, as compared with the proportion of 1 of 2.4 eyes in the Leopold and McDonald series. Besides the great discrepancy in the total number of patients treated, the following differences in the two series may be of importance: 1. Many of the Chicago series had far advanced glaucoma, and the average visual field was only 25 degrees. Did the authors' patients who failed to respond to other miotics have such changes in the field? 2. Carbachol was used most frequently prior to the institution of DFP therapy, and this miotic was not used in the Philadelphia series. 3. A concentration of 0.1 per cent DFP was tried only infrequently in the Chicago series when instillations of 0.05 per cent two or three times a day failed to control the tension.

Leopold and McDonald's observation that D F P reduced the need for miotics in 10 eyes is interesting and the effect might well be due to the breaking of peripheral anterior synechias, as they suggest. This important effect of opening the drainage angle by means of the production of intense miosis may also explain the exceptionally good results which were obtained in their cases of narrow angle glaucoma, acute glaucoma and secondary glaucoma. In these cases, in which the angles were probably blocked, DFP produced good results in 64 per cent of 98 cases in which other miotics were ineffective, as compared with the normalization of tension in 33 per cent of 161 cases of wide angle glaucoma. This factor of angle block may represent an important indication for the use of DFP. However, this consideration must be weighed against the possibility of aggravating an existent embarrassment of the angle by the engorgement of the ciliary body, a highly protein aqueous and a shallow anterior chamber, such as followed the use of DFP in 6 eyes in the authors' series. This occurred in 3 eyes in the series I am reporting, not included in the 40 eyes in the previous series. In both

eyes of 1 patient with shallow angle glaucoma, the anterior chamber was completely absent; the eyes became excruciatingly painful, although not congested externally, and the tension rose from 35 to 80 mm. (Schiotz) after the use of 1 drop of 0.05 per cent DFP twice a day for two days. Pilocarpine and phenylephrine hydrochloride (neosynephrine<sup>®</sup>) were then given locally and 50 per cent sorbitol was administered intravenously, the tension dropping to a range of 23 to 57 mm. Iridencleisis was then performed on each eye, after which the anterior chambers did not reform for two weeks. However, the tension has since remained normal, for a follow-up period of two months.

Six patients, not included in the series of the 40 eyes reviewed previously, refused to use DFP because of the symptoms it produced. Two complained of poor vision due to ciliary spasm; 2 had ocular pain, and 2, folliculosis of the conjunctiva due to hypersensitivity. None of the aphakic patients complained of discomfort.

The results in our cases have been poor, being at best only a temporary reduction of tension after other miotics had failed. In cases in which operation cannot be performed or must be deferred, DFP may be helpful. Although the infrequent need of instillation is an advantage, other miotics produce less objectionable symptoms, particularly in younger persons with good vision. DFP appears to be less effective in control of wide angle glaucoma, and it should be used in eyes with narrow angle glaucoma with caution because of the danger of immediate further embarrassment of the angle. However, DFP may be the miotic of choice in cases of aphakic glaucoma, in which it is well tolerated, or perhaps in treatment of any glaucoma in which powerful miosis is desired to open the filtration angle.

DR. RALPH RYCHENER, Memphis, Tenn.: During the past year DFP has been available to me in a limited amount, and I have had the opportunity to treat a total of 33 patients with various types of glaucoma. My results with primary glaucoma are very similar to those reported in the excellent paper by Leopold and McDonald.

In my series, I have had 3 cases of congenital glaucoma in which operation was unsatisfactory, or as yet inadvisable, and in which DFP was the only miotic which proved effective in maintaining normal intraocular pressure.

DR. ADOLPH POSNER, New York: In a series of cases of chronic simple glaucoma, I observed a number of instances in which a previously asymptomatic course was changed by the use of miotics. They were all cases of long-standing glaucoma, as evidenced by loss of field and deep cupping. The glaucoma was discovered accidentally, during routine examination. Prior to the institution of miotic therapy (usually pilocarpine) there were no subjective symptoms. Within a few months of treatment minor or major acute attacks began to develop. This indicates that DFP is not unique in producing acute attacks; miotics in general may alter the course of chronic simple glaucoma.

DR. EVERETT L. GOAR, Houston, Texas: During the past year I have been fortunate in having had available a supply of DFP, but the drug is extremely difficult to obtain unless one is connected with a medical school. Do the authors know when this preparation will be placed on the market, so that any ophthalmologist may obtain it? Several



professional colleagues in my section have borrowed from me and have not been able to pay it back. The drug has proved its usefulness and should now be made commercially available. DFP is not the answer to prayer for a cure for glaucoma, as it will accomplish only what a powerful miotic can, but it has proved its worth as an agent in the fight against glaucoma.

DR. P. ROBB McDONALD, Philadelphia: Dr. Leopold and I are both aware that there is considerable variation in the reported results with the use of DFP. When the drug was first available, like Dr. Goar, we received many requests for its use and had probably as many unfavorable as favorable replies at that time. Most ophthalmologists were looking for the wonder drug that would reduce intraocular tension. The drug was, of course, used in those cases in which everything else had failed.

Our own patients were selected from the clinics of the University of Pennsylvania Hospital and Wills Hospital and were followed by us personally. A few patients were referred to us as having uncontrolled tension, which undoubtedly would have been controlled if there had been a change in their treatment; that is, we should not have needed to resort to DFP.

Our results are considerably more promising than those of Dr. Hughes, but I think he has stated the reasons himself. Though we did not mention it in our paper, we found that the DFP is less effective in cases of advanced than of early glaucoma. In some cases of glaucoma in which the field was greatly restricted, DFP might temporarily control the tension, but a tolerance to the drug was soon evident.

We have not used carbachol to any extent in Philadelphia. We have used 20 per cent methacholine chloride (mecholyl<sup>R</sup>) in conjunction with DFP, with good effect in some cases. We have also used epinephrine bitartrate and phenylephrine in conjunction with DFP. These drugs counteract the vasodilator effect of DFP.

DFP may be an heuristic drug, as well as of some value in the treatment of glaucoma. Several interesting observations have been made. In the normal eyes its action is much longer than in the glaucomatous eye. This confirms the observation that there is a disturbance in the acetylcholine-cholinesterase balance in a glaucomatous eye. Little is known about the effect of DFP on the aqueous barrier. It may be that the primary action is there, rather than on the angle.

We believe that DFP is of value in the treatment of glaucoma. It is a drug which should be used with discretion. Both the physician and the patient should be aware of what might happen. If the tension is checked two or three hours after the first administration, acute glaucoma can probably be avoided and, if used judiciously, the drug may prove of some value.

As to Dr. Goar's inquiry when DFP will be available, all we can say is that the drug is at present under consideration by the Food and Drug Administration and that if they pass it it will be available throughout the country. The paper which we have read today may have some effect in expediting its release.

# LATTICE TYPE OF HEREDITARY CORNEAL DEGENERATION

Report of Five Cases, Including One of a Child of Two Years

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THE LATTICE type of familial corneal dystrophy was first described in 1890 by Hugo Biber,<sup>1</sup> a pupil of Haab, as *gitterige Keratitis*. He called it a chronic disease of the cornea, producing a bilateral opacity which at first looked like the residue of interstitial keratitis. The margin of the cornea was spared. Close examination revealed that the opacity was due to a lattice-like system of lines and to fine, rounded dots, which together resembled a spider's web. In regard to the lines, Biber said:

They run in various directions and sometimes cross each other. They remind one of a birch twig, branching here and there. Ledgeline projections on the surface of the cornea appear to correspond to these lines.<sup>1</sup>

Symptoms of inflammation were insignificant, and at most included slight congestion and photophobia. The disease ran a long and painless course, eventually resulting in serious impairment of vision. Biber described this condition in 3 unrelated adults, aged 39, 52 and 62 years, respectively.

Haab,<sup>2</sup> who is usually credited with first describing *gitterige Keratitis*, published a follow-up observation on Biber's cases in 1899 and included 3 new ones of his own. In Biber's cases there was a marked decrease in corneal sensitivity at that time; the periphery of the corneas was still clear, and there was no vascularization. Haab's first cases were those of a boy of 16 years and his maternal aunt and uncle. The first complaint of these patients was blurred vision; there was little or no irritation of the eyes. Haab found that the corneas were rough superficially, showed no blood vessels but exhibited a latticework of gray lines and dots. He stated:

The lines show in general a radial arrangement, especially the longer ones. Moreover, they are often forked, the work being open toward the center of the

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1. Biber, H.: Ueber einige seltenere Hornhauterkrankungen (Ulcus rodens, Keratomalacie Neugeborener, recidivierende Keratitis bullosa nach Trauma, gitterige Keratitis), Inaug. Dissert., Zurich, A. Diggelmann, 1890, pp. 35-42.

2. Haab, O.: Die gitterige Keratitis, Ztschr. f. Augenh. 2:235-246, 1899.

cornea. Still, one sees here and there a fork that is open toward the periphery. Some of the lines bend after running toward the center of the cornea, forming the arc of a large circle. The lines throughout have a somewhat undulating course, and their arrangement reminds one of twigs or the figures which one sees on a frosted window. Between the lines one sees small gray spots and points. The figures are transparent and light reflecting, so that the spots look like drops of water and the lines resemble threads of crystal.<sup>2</sup>

Pathologically, Haab noted a transparent substance deposited in and below Bowman's membrane. It was still present after the epithelium was scraped off and was considered to be a hyaline degenerative process. Haab rejected the idea that the lines were connected in any way with the distribution of the nerve fibers, nor did he believe that they were fine vessels left by a preceding interstitial keratitis. It was he who first called attention to the familial nature of the lesion.

In the same year that Haab's paper appeared (in fact, in the same volume of the *Zeitschrift für Augenheilkunde*), Dimmer<sup>3</sup> published a report of 3 siblings afflicted with the lattice-like corneal opacities. Their ages ranged from 47 to 57 years, and they had had the disease for twenty to thirty years. Dimmer found that all 3 patients had had recurrent inflammatory attacks during their youth, and he attributed this condition to rubbing of the inner part of the lid on the cornea. Pathologically, he described many punctiform hyaline and crystalline masses in the substantia propria and in Bowman's membrane. Examination of particles of these corneas revealed a colloidal or hyaline substance and triple phosphates. Dimmer's clinical description of his 3 cases was similar to those of Biber and Haab. He called attention to the fact that the lines were best seen by reflected light.

Soon after the publication of the cases of Haab and Dimmer, other reports of lattice-like degeneration of the cornea began to appear in the literature. In 1901, Hauenschild<sup>4</sup> reported a typical case. In 1902, Treacher Collins<sup>5</sup> described a typical case of reticular degeneration, although he gave it no name. Casper<sup>6</sup> described a case in 1903, calling the condition a lattice-like corneal opacity and ascribing it to trauma. In the same year, Freund<sup>7</sup> reported 15 cases, 7 in one family and 8

3. Dimmer, F.: Ueber oberflächliche gittrige Hornhauttrübung, *Ztschr. f. Augenh.* 2:353-361, 1899.

4. Hauenschild, W.: Ein Fall von gittriger Keratitis, *Ztschr. f. Augenh.* 6:139-141, 1901.

5. Collins, T.: A Case Presenting an Unusual Form of Opacity in the Central Part of Each Cornea, *Tr. Ophth. Soc. U. Kingdom* 22:148-150, 1902.

6. Caspar, L.: Gitterförmige Hornhauttrübung nach Augenverletzungen, *Klin Monatsbl. f. Augenh.* 41:289-293, 1903.

7. Freund, H.: Die gittrige Hornhauttrübung, *Arch. f. Ophth.* 57:377-399, 1903.

in another, covering four generations in each family. In 1904, Fehr<sup>8</sup> reported a case, and Spicer<sup>9</sup> described the condition in a father and his daughter and called it nodular degeneration, even though he suggested that the term, "reticular" was more appropriate. In 1907, Patterson<sup>10</sup> reported a typical case under the title "reticular opacity of the cornea." In 1908, Kipp<sup>11</sup> recorded the first case in the American literature. In 1909, Jacqueau,<sup>12</sup> in France, described 8 cases occurring in three generations of the same family.

#### DIFFERENTIATION FROM GROENOUW'S NODULAR DEGENERATION

The elucidation of lattice-like dystrophy of the cornea is complicated by the fact that Groenouw<sup>13</sup> described another, very similar, form of hereditary corneal degeneration at the same time (1890) that Biber published his report. Groenouw first discussed 2 cases of the lesion he called *knötchenförmige Hornhauttrübungen*, in a man aged 50 and in an unrelated woman aged 20. He stated:

The disease consists in the development of numerous small, rounded or irregular, gray, discrete opacities in the otherwise clear corneal tissue. The larger opacities attain a diameter of about 0.25 mm., and between them lie many smaller, dustlike, gray points. The spots are situated chiefly in the central region of the cornea and leave the margin free for the most part. The larger nodules raise the epithelium somewhat and thus give an irregular curve to the corneal surface. The opacities appear to form gradually, without inflammatory reaction, and they remain unchanged for years.<sup>13</sup>

Eight years later, Groenouw<sup>14</sup> reported on a histologic study of a small piece of cornea excised in one of these cases. He noted a foreign material deposited in discrete patches in the superficial layers of the corneal stroma, sometimes just beneath the epithelium but never within it. With hematoxylin and eosin, this material took an acidophilic stain, and he suggested a probable hyaline nature. The nuclei of the corneal

8. Fehr, I.: Ein Fall von gittriger Hornhauttrübung, *Centralbl. f. Augenh.* **28**:173-176, 1904.

9. Spicer, W. T. H.: Nodular Opacities of the Cornea in Father and Daughter, with a History of the Same in the Father's Brother and Sister, *Tr. Ophth. Soc. U. Kingdom* **24**:42-45, 1904.

10. Patterson, J. V.: A Case of Reticular Opacity of the Cornea (gittrige Keratitis, Haab), *Ophth. Rev.* **26**:223-226, 1907.

11. Kipp, C.: A Case of Grill-Like Keratitis, *Tr. Am. Ophth. Soc.* **11**:537-540, 1908.

12. Jacqueau, L.: Une forme de k ratite h r ditaire et familiale, *Clin. opht.* **15**:434-439, 1909; abstracted, *Jahresb. u. Ophth.*, 1909, p. 649.

13. Groenouw, A.: Kn tchenf rmige Hornhauttr bungen, *Arch. f. Augenh.* **21**:281-289, 1890; translated, *Arch. Ophth.* **19**:245-254, 1890.

14. Groenouw, A.: Kn tchenf rmige Hornhauttr bungen, *Arch. f. Ophth.* **46**:85-102, 1898.

cells were slightly increased in the vicinity of these deposits. He observed no significant changes in the epithelium; Bowman's membrane was largely missing, and there were no signs of inflammation. In 1917, Groenouw<sup>15</sup> reported a series of cases in three generations of this family, adding only that the process was slowly progressive, with new foci continually forming, and that the opacities increased in size by fusing with other opacities. Finally, in 1933, he<sup>16</sup> published a paper describing his observations on this process in four generations of the same family.

It was inevitable that some one should postulate that such similar corneal lesions are manifestations of the same underlying process. Fleischer<sup>17</sup> did so in 1905, in a paper in which he grouped the nodular type of Groenouw and the lattice type of Biber, Haab and Dimmer together as forms of familial corneal degeneration, the lesions varying in different cases but actually having many characteristics in common. He expressed the belief that the same etiologic factors are present in the two types. He added that the nodular type is inclined, in the course of years, to be transformed into the reticular type by the fusion of many foci. He added a new variation, the ring-shaped type, in which the opacities take the form of rings, or partial rings. This form, he stated, may be found alone, or in the same cornea with the nodular or the reticular type.

Support was soon furnished Fleischer's stand by the reported observation of the different types of opacities in the same person and, even more frequently, in the same genealogic tree. Doyne and Stephenson,<sup>18</sup> in 1905, reported 5 cases of a combined nodular and reticular type in one family. Folker<sup>19</sup> described 9 cases in three generations of a family; 7 were of the nodular type and 2 of the reticular type. Roy<sup>20</sup> reported 6 cases in the same family, in 1 of which the lattice-like configuration appeared. Weeks<sup>21</sup> described 2 cases of combined lattice and nodular keratitis in father and son. Neame<sup>22</sup> reported a case of

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15. Groenouw, A.: Knötchenförmige Hornhauttrübungen, vererbt durch drei Generationen, *Klin. Monatsbl. f. Augenh.* **58**:411-420, 1917.

16. Groenouw, A.: Knötchenförmige Hornhauttrübungen, vererbt durch vier Generationen, *Klin. Monatsbl. f. Augenh.* **90**:577-592, 1933.

17. Fleischer, B.: Ueber familiäre Hornhautentartung, *Arch. f. Ophth.* **53**:263-344, 1905.

18. Doyne, R. W., and Stephenson, S.: Upon Five Cases of Family Degeneration of the Cornea, *Ophthalmologica* **3**:213-221, 1905.

19. Folker, H.: Nodular Opacity of the Cornea in Three Generations, *Tr. Ophth. Soc. U. Kingdom* **23**:42-52, 1909.

20. Roy, D.: Report of Six Cases of Degeneration of the Cornea in the Same Family (Nodular Keratitis), *Tr. Am. Ophth. Soc.* **13** (pt. 1):101-108, 1912.

21. Weeks, J.: Family Nodular Keratitis, *Arch. Ophth.* **42**:179-180, 1913.

22. Neame, H., in discussion on Hine,<sup>23</sup> p. 45.

familial degeneration, with the reticular form in the right eye and the nodular form in the left eye. Hine,<sup>23</sup> describing the disease in a mother and her two children, said that the mother and son exhibited the nodular form, with some rings scattered among the lesions, and the daughter a pure lattice type. Gutzeit<sup>24</sup> also reported both nodular and reticular forms in the same family. Ladekarl,<sup>25</sup> combining all forms into one clinical entity, suggested that when the subepithelial deposits predominate the nodular form results, but that when most of the changes are in the superficial layers of the substantia propria the reticular form is more likely to be present. Srivinasan<sup>26</sup> reported on an interesting family with 7 cases of familial corneal dystrophy, all in female members. Three were cases of the lattice type; 2, of Groenouw's nodular form, and 2, early cases of an undetermined type. Judd,<sup>27</sup> in this country, reported 9 cases occurring in three generations of a family; both nodular and reticular forms were present. He also stated the belief that the two types were manifestations of the same process.

In 1935, Frykholm<sup>28</sup> published an extensive investigation of six generations of an afflicted family, the most complete genealogic study of the disease in the literature to date. In all, he found 42 cases of familial corneal dystrophy, involving 21 male and 21 female members. He described the clinical findings in 13 persons of the last three generations. In general, the younger persons showed the lattice-like opacities, while the older ones had the nodular type. He presented this observation as additional information that the two types are related. Freiburger<sup>29</sup> reported 11 cases, all of the nodular type except that of the youngest child, whose cornea showed some vertical streaks. Somerset<sup>30</sup> discussed 3 cases of a condition he called mixed corneal dystrophy, showing lines, nodules and ring forms.

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23. Hine, M. L.: Familial Nodular and Reticular Keratitis, *Proc. Roy. Soc. Med. (Sect. Ophth.)* **16**:43-45, 1923.

24. Gutzeit, R.: Ueber familiäre knötchenförmige Hornhauttrübung, *Ztschr. f. Augenh.* **68**:349-353, 1929.

25. Ladekarl, P. M.: Two Atypical Cases of Keratitis Nodosa Groenouw, with Histological Examinations, *Acta ophth.* **8**:213-232, 1930.

26. Srivinasan, E. V.: A Family of Groenouw's Dystrophy, *Brit. J. Ophth.* **16**:296-297, 1933.

27. Judd, J. H.: Nodular Degeneration of the Cornea, *Am. J. Ophth.* **16**:310-318, 1933.

28. Frykholm, R.: Familiäre Hornhautentartung, vererbt durch sechs Generationen: Klinisch nachgewiesen bei dreizehn Mitgliedern der dreizehn Letzen, *Klin. Monatsbl. f. Augenh.* **94**:76-106, 1935.

29. Freiburger, M.: Corneal Dystrophy in Three Generations, *Arch. Ophth.* **16**:257-270 (Aug.) 1936.

30. Somerset, E. J.: Three Cases of Corneal Dystrophy, *Proc. Roy. Soc. Med.* **30**:389-394, 1937.

## CLASSIFICATION

Bücklers,<sup>31</sup> in 1938, published the results of an extensive survey undertaken for the German government under the program for the sterilization of the unfit. He claimed that his study proved genetically and clinically that there are three distinct types of hereditary corneal dystrophy. A total of 129 affected persons from about 600 families were examined. Ninety-one cases were of the granular type; 32, of the spotty type, and 6, of the lattice-like form. Bückler's classification of the hereditary corneal dystrophies is as follows:

Nodular (or granular) type (Groenouw I).....	Dominant
Spotty (or macular) type (Groenouw II, Fuchs, Fehr and Fleischer .....	Recessive
Grill-like type (Haab, Dimmer).....	Dominant

According to Bücklers, all types begin in the first decade of life, but only the spotty form attracts attention at an early age, because of its serious effect on the visual acuity. The other two types may continue for years before the painful attacks of the lattice form, and the failing vision of the granular form, attract attention. Vascularization does not occur in any of the three forms. Ulcers of the epithelium were noted only in the lattice form, but pain and lacrimation also occurred in the macular form. Bücklers found consanguinity in all the 7 pedigrees which he investigated. However, the blood relationship was obscure in some of the pedigrees and had to be traced back eight to eleven generations. He stated that it is impossible to find combined forms and that, genetically, each type is transmitted in pure form. He also stated that only the type with double-contoured lines, with clear intervals between them, should be considered a true reticular corneal dystrophy.

Berliner,<sup>32</sup> in this country, adopted Bückler's classification and stated that under optical section the lines appear as optically empty tubes, and may be linear, fusiform, oval or round. Franceschetti and Babel<sup>33</sup> recently (1945) published a classification of hereditary and congenital corneal dystrophies, in which they adopted Bückler's system of division for the hereditary types. Von der Heydt,<sup>34</sup> discussing the types of corneal dystrophies, also endorsed Bückler's classification.

31. Bücklers, M.: Die erblichen Hornhautdystrophien, *Klin. Monatsbl. f. Augenh.* **99**:676-681, 1937; The Three Forms of Familial Corneal Degeneration and Their Hereditary Transmission, *Arch. Ophth.* **18**:331-332 (Aug.) 1937.

32. Berliner, M. L.: *Biomicroscopy of the Eye*, New York, Paul B. Hoeber, Inc., 1943, vol. 1, pp. 324-339.

33. Franceschetti, A., and Babel, J.: Essai de classification anatomique des dégénérescences familiales de la cornée, *Ophthalmologica* **109**:169-202, 1945.

34. von der Heydt, R.: Corneal Dystrophies: Types, *Am. J. Ophth.* **20**:738-740, 1937.

Mutch,<sup>35</sup> in England, published (1944) a comprehensive review of hereditary corneal dystrophies and discussed 24 cases of the granular type. He listed the following nine characteristics that the three types have in common:

1. The disease is bilateral and reasonably symmetric.
2. Onset is in the first decade of life.
3. Nodules are present, causing irregularity of the corneal surface.
4. Vascularization is absent.
5. Attacks of pain are common.
6. The central portion of the cornea is affected first, and in the dominant forms the periphery is not involved.
7. The etiologic agent is unknown.
8. The disease is resistant to any form of medical treatment.
9. It is not associated with any other known disease or defect.

Mutch also discussed the differential diagnosis of the three types, and tabulated the main points of differentiation, as follows:

Chief Differences	Granular Type	Reticular Type	Macular Type
Shape of opacities.....	Irregular, discrete granules	Interlacing lines and nodules	Spots so numerous as to form a diffuse opacity
Situation of opacities...	Axial region	Axial region	Whole cornea, denser in the axial region
Vision.....	Good until middle age	Affected early	Affected early
Hereditary transmission	Dominant	Dominant	Recessive
Corneal sensation.....	Good	Defective	Defective

No attempt is made in this paper to present the whole subject of the hereditary corneal dystrophies. The nodular form is much commoner than the lattice-like type, and many reports of the former appear in the literature. Only papers pertaining to both the nodular and the reticular form have been discussed here, in an effort to determine whether the reticular form is an entity or merely a subdivision or deviation of the commoner, nodular, type. It would seem that clinically, at any rate, the weight of opinion favors lattice dystrophy as an entity.

Additional reports on the incidence of the pure reticular form have been published as follows: Goulden,<sup>36</sup> 1 case; Zaun,<sup>37</sup> 1 case; Adrogué,<sup>38</sup> 1 case; Jeandelize and Bretagne,<sup>39</sup> 1 case; Koby,<sup>40</sup> 1 case; Caddy,<sup>41</sup> 1

35. Mutch, J. R.: Hereditary Corneal Dystrophy, *Brit. J. Ophth.* **28**:49-86, 1944.

36. Goulden, C.: Reticular Opacity of the Cornea, *Tr. Ophth. Soc. U. Kingdom* **41**:193-194, 1921.

37. Zaun, W.: Ueber die gitterige Hornhauttrübung, *Klin. Monatsbl. f. Augenh.* **72**:151-154, 1924.

38. Adrogué, E.: Lattice-Like Degeneration of the Cornea, *Rev. Soc. argent. de oftal.* **1**:32-39, 1925; *Semana méd.* **32** (pt. 2):1657-1659, 1925.

39. Jeandelize, P., and Bretagne, P.: Un cas de kératite héréditaire et familiale vu en microscopie oculaire, *Ann. d'ocul.* **163**:608-613, 1926.



case; Löwenstein,<sup>42</sup> 2 cases; Greenwood,<sup>43</sup> 5 cases; Nemeth,<sup>44</sup> 3 cases; Shapira,<sup>45</sup> 3 cases; von der Heydt and Gradle,<sup>46</sup> 1 case; Aurand,<sup>47</sup> 3 cases; Maury,<sup>48</sup> 1 case; Hruby,<sup>49</sup> 1 case; Lloyd,<sup>50</sup> 4 cases; Hesse,<sup>51</sup> 8 cases; Cavka,<sup>52</sup> 1 case; Streiff,<sup>53</sup> 1 case; Fuchs,<sup>54</sup> 8 cases; Byers,<sup>55</sup> 1 case; Pillat,<sup>56</sup> 1 case, and Hermann,<sup>57</sup> 7 cases. Altogether, 96 cases of definite lattice corneal dystrophy can be found in the literature up to the present. The 5 cases in this report make a total of 101 cases. The cases of mixed, or questionable, type that have already been noted as deviations from, or atypical forms of, Groenouw's dystrophy have not been included in this figure.

#### ETIOLOGY

Little, or nothing, is known concerning the etiology of this bizarre lesion of the cornea. Biber, Haab and Dimmer expressed no opinion as to the cause, except that it seemed to be a chronic degenerative process. Groenouw<sup>13</sup> suggested a nutritive disturbance on a hereditary basis to

40. Koby, F. E.: Sur la dégénérescence réticulaire superficielle de la cornée, Arch. d'opht. **44**:149-166, 1927.

41. Caddy, A.: Reticular Opacity of the Cornea, Proc. Roy. Soc. Med. (Sect. Ophth.) **21**:412 and 826, 1928.

42. Löwenstein, A.: Zur Klinik, Histologie und Therapie der gitterförmige Hornhautdegeneration, Klin. Monatsbl. f. Augenh. **82**:752-762, 1929.

43. Greenwood, A.: Lattice Keratitis: Studies of Four Cases Observed in One Family, Tr. Am. Acad. Ophth. **35**:248-258, 1930.

44. Nemeth, L.: Ueber die gitterige Entartung der Hornhaut, Klin. Monatsbl. f. Augenh. **95**:73-76, 1935.

45. Shapira, T. M.: Lattice Type of Corneal Dystrophy, Arch. Ophth. **14**:387-391 (Sept.) 1935.

46. von der Heydt, R., and Gradle, H. S., cited by Shapira.<sup>45</sup>

47. Aurand, D.: Trois cas de kératite en grillage observes dans la même famille, Arch. d'opht. **52**:684-685, 1935.

48. Maury, F. H.: The Pathology of Lattice and Nodular Dystrophy of the Cornea, Am. J. Ophth. **19**:866-872, 1936.

49. Hruby, K.: Gitterige Hornhautdystrophie, Klin. Monatsbl. f. Augenh. **103**:342-343, 1939.

50. Lloyd, R.: A Family with Lattice Dystrophy of the Cornea, Tr. Am. Ophth. Soc. **37**:120-126, 1939.

51. Hesse, E.: Beitrag zum Beginn und zur Erblichkeit der gitterigen Hornhautdystrophie, Arch. f. Ophth. **141**:1-19, 1940.

52. Cavka, V.: Beitrag zur familiären Hornhautdegeneration, Klin. Monatsbl. f. Augenh. **106**:348-352, 1941.

53. Streiff, E. B., cited by Franceschetti and Babel.<sup>53</sup>

54. Fuchs, E.: Ueber knöchenförmige Hornhauttrübung, Arch. f. Ophth. **53**:423-438, 1901-1902; reviewed, Ophth. Rev. **21**:187-190, 1902.

55. Byers, W.: Reticular Keratitis, Am. J. Ophth. **3**:717-721, 1920.

56. Pillat, A.: Ueber gitterige und andere Formen degenerativer Hornhauterkrankungen, Klin. Monatsbl. f. Augenh. **69**:681-682, 1922.

57. Hermann, C.: La dystrophie grillage de la cornée, Ophthalmologia **112**:350-363, 1946.

explain his nodular type. Fuchs,<sup>54</sup> discussing both types, mentioned a glandular disturbance merely as a possibility; he found an enlarged thyroid in 1 of his cases but no signs of hyperthyroidism. Wehrli,<sup>58</sup> writing primarily of Groenouw's type, observed tissue changes suggestive of tuberculous nodules and, in a single preparation, a few acid-fast bacilli, which he considered tubercle bacilli of low virulence. He therefore suggested a tuberculous basis for the disease, similar in character to lupus of the skin. Green<sup>59</sup> reported a case of severe tuberculous involvement of the skin, as well as nodular opacity of the cornea, and expressed agreement with Wehrli that the hereditary corneal dystrophies may be tuberculous. Schieck<sup>60</sup> stated that the tuberculosis was probably an associated condition. Fuchs<sup>61</sup> suggested primary hereditary degeneration of the connective tissue, allied in nature to arteriosclerosis. Byers<sup>55</sup> regarded the lines as "corrugations" of Bowman's membrane due to slight chronic hypotonicity and called the condition "anterior corrugation of the cornea."

Treacher Collins,<sup>62</sup> addressing the International Congress of Ophthalmology in 1922, included the familial corneal dystrophies with hereditary ocular degenerations (retinitis pigmentosa, macular pigmentary degeneration, amaurotic familial idiocy and Leber's [hereditary] optic atrophy), all of which he considered due to premature loss of vital force, or abiotrophy. He suggested that the corneal lesions are primary dystrophies of the corneal nerves and end organs, followed by thickening of the neuroglial tissue surrounding the nerves, hyaline degeneration and formation of spaces filled with coagulum, representing those previously filled with nerve tissue. If the nerve fibers are particularly involved, the lattice-like variety is the end result; if the end organs are primarily affected, the nodular form develops.

Pillat,<sup>56</sup> in agreement with Collins, stated that the primary causative factor is a degenerative process affecting the trigeminal nerve. In his

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58. Wehrli, E.: Die knötchenförmige Hornhauttrübung Groenouw<sup>13</sup>) eine primäre isolierte, chronische, tuberkulose Erkrankung der norderen Schichten der Cornea: Lupus Cornea, Ztschr. f. Augenh. **13**:322-334, 1910; Weitere klinische und histologische Untersuchungen über den unter dem Bilde der knötchenförmige Hornhauttrübung (Groenouw<sup>13</sup>) verlaufenden chronischen Lupus der Hornhaut, Arch. f. Ophth. **55**:126-184, 1906.

59. Green, J.: Nodular Opacity of the Cornea, with Special Reference to Its Etiology, J. A. M. A. **53**:920-924 (Sept. 18) 1909.

60. Schieck, F.: Die Degenerationen der Cornea, in Schieck, F., and Bruckner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 4, pp. 398-403.

61. Fuchs, A.: Zur Kenntnis der gitterigen Hornhautentartung: Haab-Dimmer, Ztschr. f. Augenh. **57**:159-186, 1925.

62. Collins, T.: Hereditary Ocular Degenerations: Ophthalmic Abiotrophies, Tr. Internat. Cong. Ophth. **1**:103-143, 1922.

case, he reported a reduction of sensibility over an area supplied by the ophthalmic and maxillary branches of the fifth nerve, as well as a highly reduced corneal sensitivity. He expressed agreement with Collins as to the mode of production of the two forms and explained the lesion as a primary neurotrophic disturbance, followed by secondary necrobiosis. According to Pillat, when the nerve fibers and the terminal plates are both involved, the mixed variety, or reticulonodular form, results. Gutzheit<sup>24</sup> also advocated Pillat's neurotrophic disturbance as the cause.

Kraupa,<sup>63</sup> working in the Elschmig clinic, also agreed with Collins that the primary cause was neurotrophic and claimed that the lesions were demonstrable changes resulting from degeneration of the corneal nerves. Koby,<sup>64</sup> in his book on biomicroscopy of the eye, stated that reticular keratitis is due to chronic inflammation of the corneal nerves. He also offered folds or ruptures in Bowman's membrane as an etiologic possibility. Löwenstein,<sup>65</sup> working in the Elschmig clinic but pursuing his investigations independently, came to the same conclusions as Collins, Pillat and Kraupa.

However, Stanka,<sup>66</sup> another member of the Elschmig staff, stated his disagreement with Kraupa and Löwenstein and claimed to have proved that the grillwork is not connected with the corneal nerves. According to Stanka, the central portion of the cornea is so extensively damaged that it could not possibly be secondary to a neural degeneration. If it were, the corneal sensitivity, he stated, should always be totally abolished, whereas it is usually only moderately reduced, or even normal. Moreover, Stanka said he could demonstrate by vital staining that there was never a direct contact between the nerves and the degenerative foci. By means of the slit lamp, he detected a decrease in the number of limbal capillaries and frequent aneurysms at the bifurcation of the limbal vessels. Stanka concluded that failing nutrition of the cornea, due to these anomalies, was the primary causative factor.

#### PATHOLOGIC FEATURES

Since the total number of cases of lattice dystrophy reported to date is small, and because few eyes so afflicted are likely to reach the pathologic laboratory, knowledge of the pathologic characteristics is meager.

63. Kraupa, E.: Die familiär degenerativen Hornhautveränderungen im System des sogenannten Dystrophien der Hornhaut, *Klin. Monatsbl. f. Augenh.* 70:397-398, 1923.

64. Koby, F.: *Slit Lamp Microscopy of the Living Eye*, Philadelphia, P. Blakiston's Son & Co., 1925, p. 103.

65. Footnote deleted.

66. Stanka, R.: Ueber familiäre gitterige Hornhautdegeneration, *Klin. Monatsbl. f. Augenh.* 7:357-360, 1925.

Haab and Dimmer reported discrete deposits of hyaline-like material in the anterior third of the stroma and in Bowman's membrane. Freund<sup>7</sup> observed the same deposits of hyalin and absence of Bowman's membrane.

Fuchs,<sup>67</sup> in 1915, published the results of his thorough study of the nodular form. He described two primary changes: (1) a subepithelial secretion of an acidophilic substance, and (2) a basophilic substance in the superficial layers of the corneal stroma. He also noted fissure formation, epithelial overgrowth, thinning and disturbances of Bowman's membrane and swelling and partial disappearance of the corneal lamellas. These two staining reactions were not confirmed until 1940, when Löwenstein<sup>68</sup> reported similar findings in 3 cases of nodular dystrophy: acidophilic material anterior to Bowman's membrane and basophilic masses in the anterior stroma. He emphasized that the distinction between the two substances was perceptible only in those places where Bowman's membrane was preserved.

Paderstein<sup>69</sup> stated that the nodular form of Groenouw is a primary degeneration of the epithelium: The nuclei are destroyed, and the protoplasm is changed into a hyaline substance, which tends to accumulate on the surface of Bowman's membrane. In his case, the pathologic changes were observed exclusively in the epithelium, anterior to Bowman's membrane, and the stroma was unaltered. Puscarin,<sup>70</sup> Uhthoff<sup>71</sup> and Wirth<sup>72</sup> also described epithelial changes similar to those of Paderstein. Fuchs<sup>54</sup> stated the opinion that the flattening of the epithelium above the nodules and the destruction of Bowman's membrane were purely mechanical changes caused by the pressure. Ladekarl<sup>25</sup> stated that the epithelial changes were too pronounced to be considered secondary changes due to mechanical pressure.

The first complete pathologic examination in a case of lattice dystrophy was that of Maury,<sup>48</sup> in 1936. His patient had had an optical iridectomy by another ophthalmologist, followed by extraction of a postoperative cataract. After the extraction, the eye became painful, shrunken and

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67. Fuchs, E.: Ueber knötchenförmige Hornhauttrübungen, *Arch. f. Ophth.* **89**:336-349, 1915.

68. Löwenstein, A.: Glass Membranes in the Eye, *Am. J. Ophth.* **23**:1229-1242, 1940.

69. Paderstein, R.: Bemerkungen zu Wehrli's Kritik meines Falles von knotchenförmiger Hornhautdegeneration, *Klin. Monatsbl. f. Augenh.* **47**:156-167, 1909.

70. Puscarin, E.: Deux observations d'opacité nodulaires de la cornée (Maladie de Groenow), *Arch. d'opht.* **33**:362-373, 1913.

71. Uhthoff, W.: Weitere klinische und anatomische Beiträge zu den degenerativen Erkrankungen der Hornhaut, *Klin. Monatsbl. f. Augenh.* **55**:290-299, 1915.

72. Wirth, M.: Zur Histologie der knötchenförmigen Hornhauttrübung, *Ztschr. f. Augenh.* **58**:106-114, 1926.

blind, and enucleation was carried out. Immediately after the enucleation, the cornea was divided into numerous sections so that different portions could be subjected to different histologic technics. A study of one portion, with supravital staining with methylene blue, revealed that the lattice fibers were in no way connected with the corneal nerves. Another portion, subjected to the Bielschowsky silver stain, also revealed no relation between the nerves and the opacities, although both were well impregnated with silver. Frozen sections were stained with strong solution of iodine U. S. P., and a negative reaction for amyloid was obtained.

Frozen sections, both fixed and unfixed were stained with sudan III (C. I. No. 248) for fat. The nodular and lattice opacities had a homogeneous red appearance with this stain, and minute deposits, invisible with other stains, were readily seen in these sections. In the smallest lesions, the hyalin-lipid deposits could be clearly seen within the fibers of the corneal stroma. In the central zone of the cornea, Bowman's membrane stained with sudan III in several places.

With hematoxylin and eosin, the corneal opacities appeared as pink-staining, hyalin masses, sometimes homogeneous and sometimes laminated. With the Van Gieson stain, the masses took a light yellow tint. With Mallory's stain for connective tissue the deposits were colored orange, in sharp contrast to the blue-staining normal corneal lamellas. The best differentiation was obtained in a portion fixed in solution of mercury bichloride U. S. P.; the involved corneal corpuscles were scanty, and those that were seen appeared small and shrunken. The uninvolved corneal lamellas appeared normal. No hyalin deposits were seen in the epithelium. Maury concluded that the primary lesion was a deposition of hyaline material in the corneal corpuscles themselves.

Another good pathologic description of the lattice form is found in the paper of Franceschetti and Babel,<sup>33</sup> in which they described sections loaned to them by Prof. E. B. Streiff. They found the epithelium involved: thickened in some places, thin in others and flattened out completely in still other aspects. Bowman's membrane was destroyed for the most part. Where it was present, it was separated from the epithelium by a little connective tissue. In the anterior layers of the stroma, these authors noted thickened, hyalinized lamellas. There was a great abundance of deposits and granulations, of such variable shapes that the normal structure of the lamellas was destroyed. The smallest deposits were seen in the interior of the lamellas; the largest ones had destroyed the lamellas completely. Many of the deposits were subepithelial.

Franceschetti and Babel reported that all the granulations were strongly basophilic, that they were partially stained with gentian violet and that they stained brownish yellow with strong solutions of iodine U. S. P. Stained with hematoxylin and eosin, the pink-staining masses

were not homogeneous; the centers were darker. With the Masson trichrome stain, there was seen double staining: red and green. With the Van Gieson stain the masses were black, and with Mallory's stain, a deep red. They stated the belief that the hyalinized thickened lamellas seen throughout the parenchyma were probably the anatomic basis for the lattice fibers and that the basophilic masses were the nodules.

In 1946, Hermann<sup>57</sup> published an excellent clinical and pathologic description of 7 cases, all occurring in one family. Pathologically, the epithelium was observed to be very irregular, being thick in some places and very thin in others. The polyhedral and basal cells were completely gone; only flat, squamous-like cells were present. Bowman's membrane was not present; in its place, numerous amorphous masses were seen, causing "bumps" which pushed into the epithelium. Similar masses were seen in the anterior layers of the stroma. Many of the corneal fibers in these layers were swollen and degenerated; there were no signs of inflammation. With the trichrome stain, the masses were red; with the Van Gieson stain, yellowish, and with hematoxylin and eosin, pink. There was no trace of lipid deposits. The May-Greenwald-Giemsa stain revealed two types of masses: the first, red, were extremely small and were located inside the superficial lamellas of the cornea; the second, blue, were larger and variable in size and were observed subepithelially and between the corneal lamellas. Hermann found the optically empty tubes, as described by Bücklers, only in the early stages; later the tubes became filled with the hyalin material and were refractile.

#### TREATMENT

Diseases of unknown etiology and obscure pathology are usually difficult to treat, and that is certainly true of the familial dystrophies. Therapy in most cases has been merely palliative and expectant, although a great variety of medicaments have been tried, empirically. Iodides, preparations of mercury and tuberculin have been used systemically. As drops, zinc sulfate, boric acid, silver nitrate, potassium iodide, resorcinol and colchicum have been instilled. Iodoform, ethylmorphine hydrochloride, jequiritol and mild mercurous chloride U. S. P. have been used as dusting powders. Yellow mercuric oxide, ichthammol and boric acid have been prescribed in ointment form. Use of thyroid and ovarian extracts, vitamin A, liver and iron has been unsuccessful. Heat and cold have been tried by many. Some have attempted to increase the nourishment of the cornea by subconjunctival injections of irritating substances. Protein shock was tried by one author.

A variety of surgical procedures have been performed, but usually with no more success than met the medical measures. Superficial curettage of the cornea was the first operation employed (Haab, Dimmer

Groenouw), but most authors reported unfavorable results. Verhoeff,<sup>73</sup> however, reported beneficial results from this procedure in 3 cases. Optical iridectomy has been done in a considerable number of cases. Bücklers examined several patients who had had optical iridectomies but found the visual acuity unimproved and the patient more uncomfortable because of the dazzle and colored vision that ensued. Other operations that have been tried are paracentesis, cauterization, sympathectomy, grafting of mucous membrane from the lip and corneal transplantation. Although it is commonly thought that the dystrophy eventually invades the graft, Franceschetti and Streiff<sup>74</sup> favored this type of operation. Keratoplasty was performed on one eye in each of 3 of the cases reported in the present paper, with favorable results in 2 cases to date, but there is no assurance that the degeneration will not invade the transplanted tissue in time.

#### REPORT OF CASES

**CASE 1.—History.**—Mrs. V. F., a white woman aged 35, came to the department of ophthalmology of the Vanderbilt Clinic on March 5, 1947, with the request that her 2 year old son (case 2) be treated for an hereditary corneal disease. She stated that her father, one sister, one brother and she herself had had some type of chronic corneal disease as long as she could remember. Figure 1 is the pedigree of this family, showing the afflicted and the nonafflicted members. She said that all 4 of them had been "doctoring" for this ocular trouble all their lives, but all forms of therapy had been unsuccessful. She was greatly upset that her young son began to show evidence of the same process.

Mrs. V. F.'s ocular disease began at the age of 3 months, according to her mother, with recurrent attacks of "inflammation of the eyes," lasting from two to four days. The attacks evidently consisted of conjunctival injection, tearing and photophobia. For many years the episodes recurred about once a month, but since her reaching maturity they had become progressively less frequent. At the time of this report, she had an attack about every six months. The last one was approximately six weeks before her visit to the clinic. She stated that with the passage of time the attacks seem also to have become less severe.

The patient was unable to date exactly the beginning of her loss of vision. She stated that vision had gradually, but constantly, decreased through her school years. She was able to read through the grade school years and finished grade school satisfactorily. She could not see well enough to go on to high school and has not been able to read print of any size for the past fifteen years.

During her youth she was a frequent patient at two of the larger eye clinics on the eastern coast and at various other general clinics. She stated that she had had an intensive laboratory investigation, including blood tests, cutaneous tests and roentgenographic studies of the chest, but that no cause for her disability had been found.

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73. Verhoeff, F. H., discussion on Lloyd,<sup>50</sup> p. 125.

74. Franceschetti, A., and Streiff, E. B.: Hereditary and Constitutional Dystrophies of the Cornea, in Ridley, F., and Sorsby, A.: *Modern Trends in Ophthalmology*, London, Butterworth & Co., Ltd., 1940, pp. 419-420.

Her general medical history was not unusual. She had had measles and mumps as a child, and mild sinusitis for many years, without operation on the sinuses. Her appendix was removed in 1940. She had nephritis in 1945; there were no sequelae. Her menstrual history was within normal limits. She had two miscarriages before her baby was born. She stated that they were spontaneous, and she could give no contributory data. She had a normal pregnancy and delivery in 1945, uncomplicated except for the mild nephritis.

*Ophthalmologic Examination.*—Vision: Vision was limited to counting fingers at 1 foot (30 cm.) in her right eye and to perception of hand movements at 1 foot in her left eye. Light projection was accurate in both eyes. The conjunctivas and lids were normal in appearance. Tension was normal to palpation in both eyes.

Corneas: Macroscopic examination revealed diffuse white opacity of almost the entire cornea of each eye. The opacification was so dense in the pupillary area that the iris and the pupil could not be seen. Peripherally, there was a band, about 1 mm. in width, adjacent to the limbus, which was considerably clearer than the central portion of the cornea. The iris could be seen through this portion of the

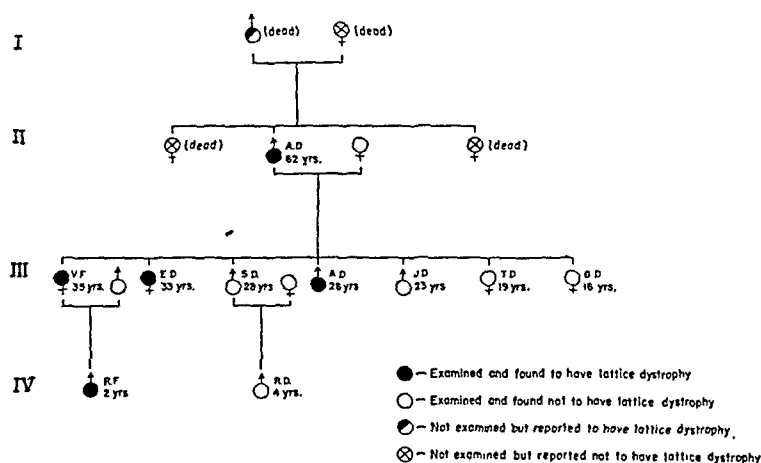


Fig. 1.—Diagram showing the pedigree of the afflicted family.

cornea and appeared to undergo normal movements when light was flashed into the eye. With the loupe and with good reflected illumination, a fine network of white lines, with many fine white dots in the interstices, could be seen. Viewed in this manner, the opacity gave one the impression of looking at a cobweb. The corneal sensitivity was moderately reduced in the left eye and greatly reduced in the right eye. There was no staining of the epithelium with fluorescein.

On microscopic examination with the slit lamp, the lattice-like network was not so obvious. In any one part of the beam a few lines were seen. The lesion consisted mainly, however, of myriad discrete, white deposits in all layers of the cornea, being much heavier in the anterior third than posteriorly. Here and there, larger deposits, which seemed to be accumulations of the smaller dots, were visible. The small, discrete dots were seen in the epithelium, but no lines were apparent there. The lines showed no definite pattern but seemed to run in all directions; some branched dichotomously, and all appeared to consist of the same refractile substance as the dots. It was difficult to study the lines with direct illumination; they were best seen with diffuse reflected light and were seen more easily in the peripheral parts of the opacity, where the iris began to show through. No blood vessels were seen in any portion of the cornea of either eye. The surface of the



epithelium was smooth, and there were no protrusions or breaks in its contour. However, its luster seemed much decreased. Figure 2 *A* is a drawing of the cornea of the right eye of this patient as seen with the slit lamp.

The anterior chamber and lens could not be observed in either eye because of the opacities in the cornea. The pupils, as seen through the periphery of the cornea, seemed to possess normal reactivity. The fundi could not be visualized. Transillumination showed nothing abnormal in either eye.

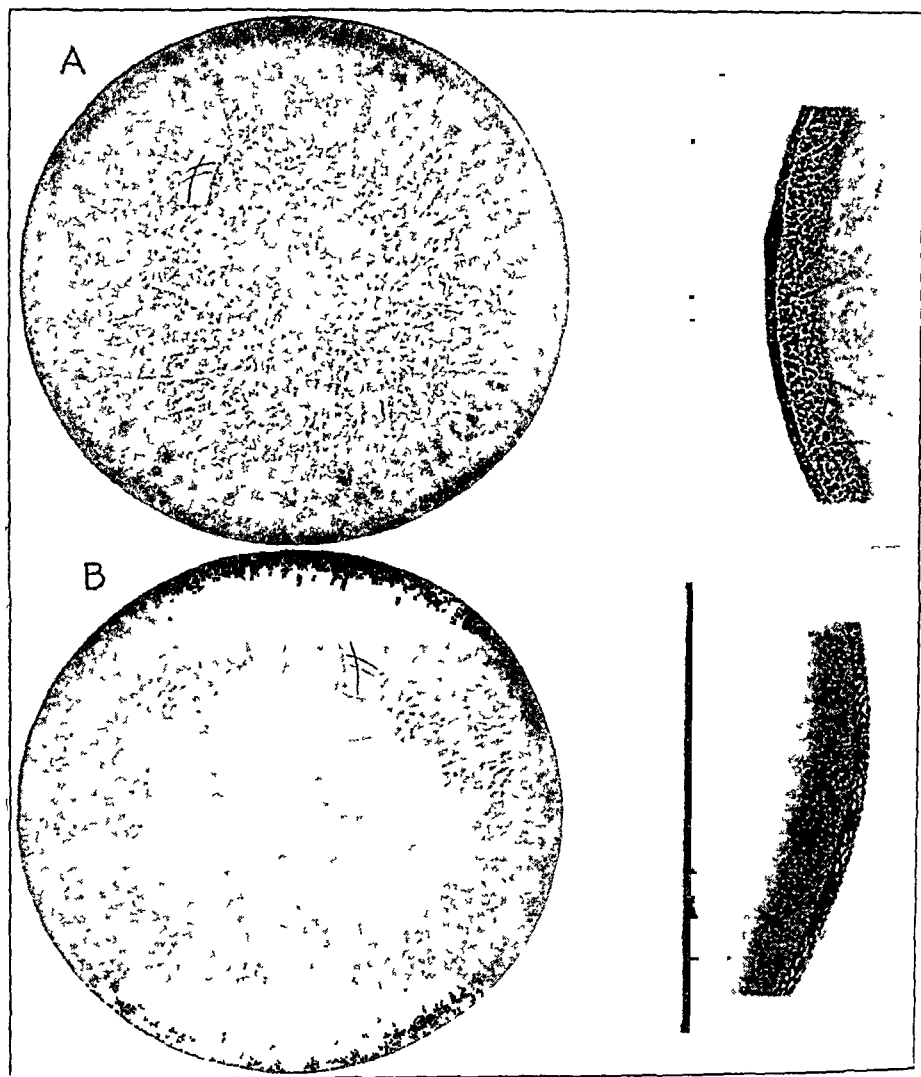


Fig. 2.—*A* (case 1), drawings of the cornea of the right eye taken with the slit lamp. *B* (case 3), drawings of the cornea of the left eye taken with the slit lamp.

A diagnosis of corneal dystrophy of the Haab-Dimmer type was made. Corneal transplantation, with a guarded prognosis, was suggested and was accepted eagerly by the patient.

Manifest refraction was  $-1.00$  sph.  $\ominus -3.50$  cyl., axis 15 in the right eye; she read the 10/200 line with this eye. Vision in the left eye was not improved with lenses; she read the 2/200 line. There was no further improvement with the pinhole disk.

*Operation and Subsequent Course.*—On June 2, 1947, the patient was admitted to the Institute of Ophthalmology for cornea transplantation. General physical examination at that time revealed no defects except the corneal dystrophy. On the day following admission, a 5.5 mm. penetrating keratoplasty was performed, a specimen 5.5 mm. square being removed. The specimen was sent to the pathologic laboratory for sectioning, but the final result was not satisfactory. It was evident, however, that this specimen showed the same type of pathologic changes as are described in case 4. When the sutures were removed, one week after operation, the anterior chamber was flat and the iris was adherent to the graft nasally. The graft was flat but cloudy. Separation of the adhesions of the iris was then performed by means of cyclodialysis approach, and a conjunctival flap was brought down over the cornea. When the flap receded, the graft was clear, but the anterior chamber was still flat. There was no evidence of a leak with the fluorescein test. On her discharge from the hospital, six weeks after the keratoplasty, the anterior chamber was still flat, and there were anterior synechias below and temporally. Vision was not determined at this time.

She was readmitted to the hospital, and another synechiotomy (by cyclodialysis approach) was attempted on Aug. 25, 1947. The synechias recurred, however; the anterior chamber remained filled with blood, and secondary glaucoma ensued. On Sept. 3, 1947, a cyclodiathermy operation was performed. The tension remained within normal limits after this procedure, and the patient was again discharged. At the time of her most recent visit to the clinic (June 7, 1948), a ciliary staphyloma was developing in the eye which had been operated on; the graft was opaque, and there was no light perception.

CASE 2.—R. F., a 2 year old white boy, the son of Mrs. V. F. (case 1), began to have attacks of "sore, red eyes" soon after his birth, his mother stated. The attacks, which consisted of pain in the eyes, lacrimation and severe photophobia, lasted from two to four days and recurred every three to four weeks. The attacks were usually first noticed in the morning, on rising. The child would not open his eyes, but kept them tightly closed for the duration of the episode, and insisted that all the window shades in the room be drawn. He preferred to stay in bed, had no appetite and was very irritable during the attack, although he was normally a pleasant child.

Careful examination was impossible at the first visit to the clinic because of lack of cooperation on the part of the child. However, he was "mummified" on the examining table; "pontocaine" (tetracaine U. S. P.) was instilled into the conjunctival sacs, and his eyes were opened by means of lid retractors. With a loupe, it was seen that he had some type of corneal opacity in both eyes, but the exact nature of the lesions could not be determined. He was referred to the department of pediatrics for a general examination, and his mother was requested to bring him to the hospital during one of his "attacks" for examination under ether anesthesia.

General physical examination by the pediatrics department revealed an entirely normal, well developed, well nourished, attractive-appearing child, without defect except for his eyes. The blood count and urine were normal. The Schick, Mantoux and Kline tests gave negative reactions.

Two weeks later, the child was brought to the clinic during an attack and was admitted to the Institute of Ophthalmology for observation and examination.

*Ophthalmic Examination.*—No visual test was obtained because of the patient's age and condition. According to his parents, he had no apparent visual difficulty except during his attacks. Both eyes were tightly closed, and he strongly resisted any attempt to open them. With the aid of tetracaine and lid retractors, a brief survey was made. The palpebral conjunctiva was moderately injected. The bulbar conjunctiva was white, and there was no ciliary congestion. The corneas appeared grossly clear. The anterior chambers were clear and of normal depth. Pupillary responses were normal. The eyes were straight, and the excursions seemed full. The fundi could not be visualized.

The patient was then given ether anesthesia by the open drop method in the treatment room. As soon as he was in deep anesthesia, he was held up before the corneal microscope by a nurse and the anesthesia continued as well as possible.

The central portion of each cornea was found to contain a fine network of white lines, in the interstices of which were a number of minute, discrete, white dots of a refractile substance. The process involved the whole cornea except for a clear area around the limbus. The deposits appeared to be subepithelial and were limited to the anterior third of the cornea. The size of the deposits was not constant: Most of them were fine and of approximately the same size and shape; a few were several times as large as the average. These larger deposits, in some cases, seemed to invade the epithelium. No blood vessels were seen in either cornea. The surface of the epithelium appeared normally smooth and regular except for one area near the center of the cornea in each eye, where the surface looked rough and broken. This rough spot was superimposed on a large, fresh-looking, yellowish deposit that protruded into the epithelium from the superficial layers of the stroma. On completion of examination with the slit lamp, the child was placed on an examining table and fluorescein instilled into each eye. The rough areas previously seen with the microscope stained a bright green.

The lines in the cornea were seen much better in this patient than in his mother (case 1) because there was much less deposition of the foreign material in the cornea. Whereas the round deposits in the mother's cornea were so numerous as to form an almost homogeneous mass in the center, they were discrete and scattered in the son's. The iris and pupil could easily be seen in the boy, and they provided a dark background that helped to clarify the lines and deposits. Viewed against this background, some of the lines gave the effect of a hollow tube, described by Bücklers and Berliner. These appeared as double lines, with an optically clear interval between. The lines crisscrossed over the cornea in no definite pattern: Some were long; some were short; some branched, and some did not. Macroscopically, neither the lines nor the nodules could be seen.

The patient recovered from the anesthesia uneventfully, and the following day he was discharged from the hospital. A diagnosis of the Haab-Dimmer type of corneal degeneration was made. Treatment can be only palliative in patients of this age group.

CASE 3.—Miss C. D., a white woman aged 32, is the sister of Mrs. V. F. (case 1). According to her mother, she began to have attacks of red, sore eyes at about 5 months of age. These had recurred regularly at monthly intervals for many years. The patient attended regular grade school and completed the eight grades satisfactorily, although she attended sight conservation class for one year (fifth year). In her early teens, she was able to read books and newspapers. She wore glasses through the school years and expressed the belief that she was near sighted. When 18 years of age, the patient inadvertently took too many

sleeping tablets and had to be taken to the hospital to have her stomach "washed out." She dated her loss of vision from that episode, stating that her visual acuity deteriorated rapidly the following year. She was taken many times to various ophthalmologic clinics, together with her sister, but had had progressive loss of vision for the fourteen years prior to her present visit.

Her general medical history was noncontributory so far as the disease of the eyes was concerned. She had measles and mumps as a young child, and bronchopneumonia at 5 years of age. An appendectomy was performed in 1933, and operations for bilateral hallux valgus were done in 1939. In 1940 an optical iridectomy was done on the left eye, without appreciable increase in vision. In 1942 an ovarian cyst was removed, and in 1945 bilateral partial oophorectomy and salpingectomy were performed. She stated the belief that the latter operations were for adhesions.

*Ophthalmologic Examination.*—Vision was limited to perception of hand movements at 2 feet (60 cm.) in each eye. Light projection was accurate in both eyes. Tension appeared normal in both eyes on palpation. Transillumination revealed nothing abnormal in either eye. The conjunctivas and lids were normal in appearance.

*Corneas:* Macroscopic examination revealed a diffuse white opacity of most of the cornea of each eye; peripherally there was a narrow clear band. The opacity in the pupillary area was so dense that neither the iris nor the pupil could be seen. The iris could be observed through the peripheral clear area, and apparently the pupillary reactions were normal. A wide iridectomy, from 12 to 3 o'clock had been performed on the left eye. The corneal sensitivity was considerably reduced in each eye. There was no staining of the epithelium with fluorescein.

With the corneal microscope, the same lattice-like network of lines and dots was seen in this patient's corneas as was exhibited by her sister. The lesion was so dense centrally that it assumed the appearance of a homogeneous white mass. As one left the central area, however, the discrete, white deposits become less concentrated and the lines become evident. In the portion of the periphery which appeared clear and transparent grossly, the lines and dots were greatly reduced in number but were still present. As in the previous 2 cases, the foreign material was largely found in the anterior third of the cornea, the stroma becoming progressively clearer as one looked posteriorly. No blood vessels were found in either eye. Figure 2B is a drawing of the cornea of the left eye of this patient made with the slit lamp.

*Manifest Refraction:* There was no improvement with lenses in either eye. She saw only hand movements with either eye. There was no further improvement with pinhole disks.

A diagnosis of familial corneal degeneration of the Haab-Dimmer type was made. The case was considered unfavorable for corneal transplantation, but an attempt to improve the patient's vision by the operation was considered justified because of the degree of her visual loss.

*Operation and Subsequent Course.*—The patient was admitted to the Institute of Ophthalmology and a keratoplasty performed on her right eye, a specimen 5 mm. square being removed. Unfortunately, the tissue was not saved for pathologic examination. During her convalescence from the operation, she had one of her "attacks" in the left eye. Examination revealed mild conjunctival injection, tearing and moderate photophobia. Staining with fluorescein revealed

an irregular abrasion of the center of the cornea, very similar to the one seen in her nephew (case 2). Examination with the slit lamp showed a large, fresh-looking, amorphous, yellow deposit in the epithelium and anterior layers of the substantia propria. The remainder of the corneal surface was unchanged. This ulceration healed over in three days, and her symptoms disappeared.

On her discharge from the hospital, vision in the right eye was 20/70 with a pinhole disk. Figure 3 contains photographs of the eyes before and four weeks after the operation. Two months after discharge, manifest refraction was  $-6.00$  sph.  $\ominus -6.00$  cyl., axis 103 in the right eye. She read 20/50 easily. Four months after the operation, the graft was still clear and vision with correction unchanged.

Eighteen months after operation, vision in the right eye was reduced to 12/200, with a correction of  $-9.00$  sph.  $\ominus -6.00$  cyl., axis 105. The graft was still clear but evidenced a tendency to bulge forward.

CASE 4.—Mr. A. D., a white man aged 61, the father of the patients in cases 1 and 3, was born in Italy but had been in the United States for forty-three years.



Fig. 3 (case 3).—The right eye, four weeks after operation. The left eye is shown for comparison because no photographs were taken of the right eye before operation.

He remembered that his father always suffered from "bad eyes," and he expressed the belief that this was due to the same type of disease that he and 4 members of his family now had. The father died forty-one years ago. The mother was not afflicted.

The patient's story was very similar to that of his daughters. He had had frequent attacks of "sore, red eyes" ever since he was a baby. During his childhood, they recurred every three or four weeks and were so painful that "he threw himself on the ground and cried." He was uncertain about the date of his beginning to lose his vision, but he remembered that he had visual difficulty at about 21 years of age and that at 30 he was going to doctors for glasses to improve his sight. For the past thirty years, visual acuity had undergone a steady, progressive decrease. He had always worked as a laborer.

There was nothing remarkable in his general medical history. He had had the usual childhood diseases, but did not remember specifically which. He had one attack of pleurisy when a young man but had had no other evidence of tuberculosis. Bilateral optical iridectomy was performed in 1940. He had had bronchial asthma for the past ten years.

*Ophthalmologic Examination.*—Vision was counting fingers at 2 feet (60 cm.) in the right eye and was 4/200 in the left eye. Light projection was accurate in both eyes. The tension was normal to palpation in both eyes. Transillumination revealed nothing abnormal in either eye. The conjunctiva and lids were normal in appearance.

*Corneas:* Macroscopically, there was a diffuse white opacity of each cornea, similar to that in the previous cases. In one feature it differed from that of the daughters. A group of prominent large white lines ran radially and roughly

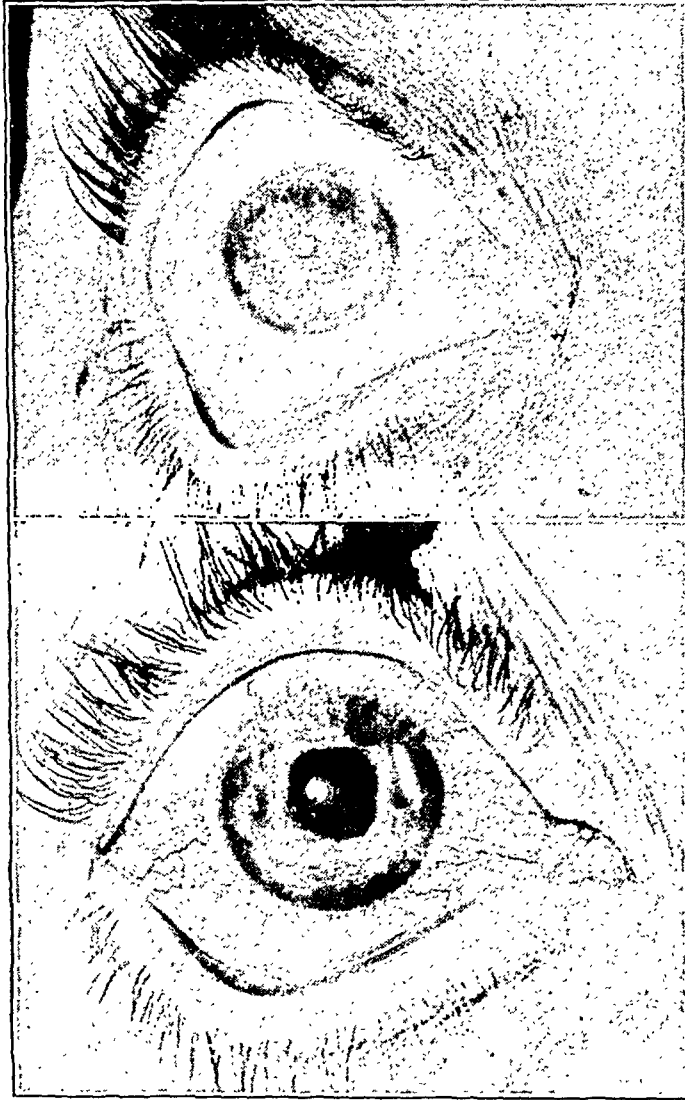


Fig. 4 (case 4).—Photographs of the right eye before and one month after operation.

parallel in the upper part of each cornea. These seemed exactly like the other lines when studied microscopically, except that they were larger and were easily seen with the naked eye. The periphery was again relatively clear. The corneal sensitivity was reduced in both eyes. There was no staining of the epithelium.

Microscopically, the lattice effect of the lines was more obvious in this patient than in the others. There were many lines, easily seen with reflected illumination and a low power objective in the microscope, which ran together to form a lacelike design throughout the cornea. The lines and dots were again found predominantly

in the anterior third of the corneal stroma. The center contained the greatest concentration of the foreign material, and it was so dense that the pupil could not be seen. Peripherally, the iris could be seen, and apparently reacted normally. The results of wide basal iridectomies could be made out above in each eye. No blood vessels were seen in either eye. The surface of the epithelium was normally smooth, but lacking in the usual luster of healthy epithelium.

**Manifest Refraction:** Vision was not improved with lenses, and was limited to hand movements in each eye. There was no further improvement with pinhole disks.

**Operation and Result.**—A diagnosis of the lattice type of corneal dystrophy was made. The patient was anxious to have a transplantation because of the good results in his daughter's case. He was admitted to the Institute of Ophthalmology, and keratoplasty was performed on his right eye, a specimen 5 mm. square being removed. The pathologic specimen was carefully preserved and sent to the laboratory for examination. Figure 4 shows photographs of this patient's right eye before and one month after the operation. Two months after his discharge, manifest refraction for the right eye was  $-5.50$  sph.  $\ominus -1.50$  cyl., axis 155, and he read 20/50 easily. This correction was prescribed, and three months after operation the graft was still clear and corrected vision unchanged.

Fourteen months after operation, the patient was complaining of decreasing vision. Vision in the right eye (with his glasses) was 20/100. Refraction was not obtained prior to publication.

**Pathologic Examination.**—The specimen was a section of cornea, about 5 mm. square. The posterior surface had shrunk, however, so that it is only about 2 mm. long. This had caused the ends of the epithelial surface to bow posteriorly, in the manner typical of transplantation specimens. The cornea appeared much thicker than normal, but this may have been an artefact, due to the wrinkling of the posterior layers. Figure 5 shows three sections of the specimen stained with hematoxylin and eosin, the Masson trichrome method and the Van Gieson method.

The epithelium was of irregular thickness (fig. 5 *A*). In some places it consisted of only three layers of cells, and in others it was stratified and composed of eight to ten layers. In the thickest places, the basal layer was composed of high columnar cells, which were pale and appeared hydropic. In the area of intermediate thickness, the basal layer was made up of cuboidal cells, similar in appearance to the columnar type. In the thinnest parts of the section, there was no basal layer; the epithelium consisted of merely a few layers of flat, horizontal, squamous-like cells. In the places where the columnar and the cuboidal basal layers were present, there were no intermediate, or wing, cells of Salzmann; the transition was abrupt, from tall to flat cells. The normal architecture of the epithelium was totally destroyed throughout the sections.

In the sections stained with the Masson trichrome method, there was an unusual staining arrangement of the epithelium. The superficial layers of the epithelium had taken a deep red stain, identical with the red-staining material in the anterior

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Fig. 5 (case 4).—Low power magnifications of three sections from the pathologic specimen obtained. *A*, section stained with hematoxylin and eosin, showing well the irregularity of the epithelium. *B*, section stained with the Masson trichrome stain, showing general distribution of the foreign material; the dark anterior portion of the cornea stained almost solidly dark red with this stain. *C*, section stained with Van Gieson's stain, showing little at this magnification.

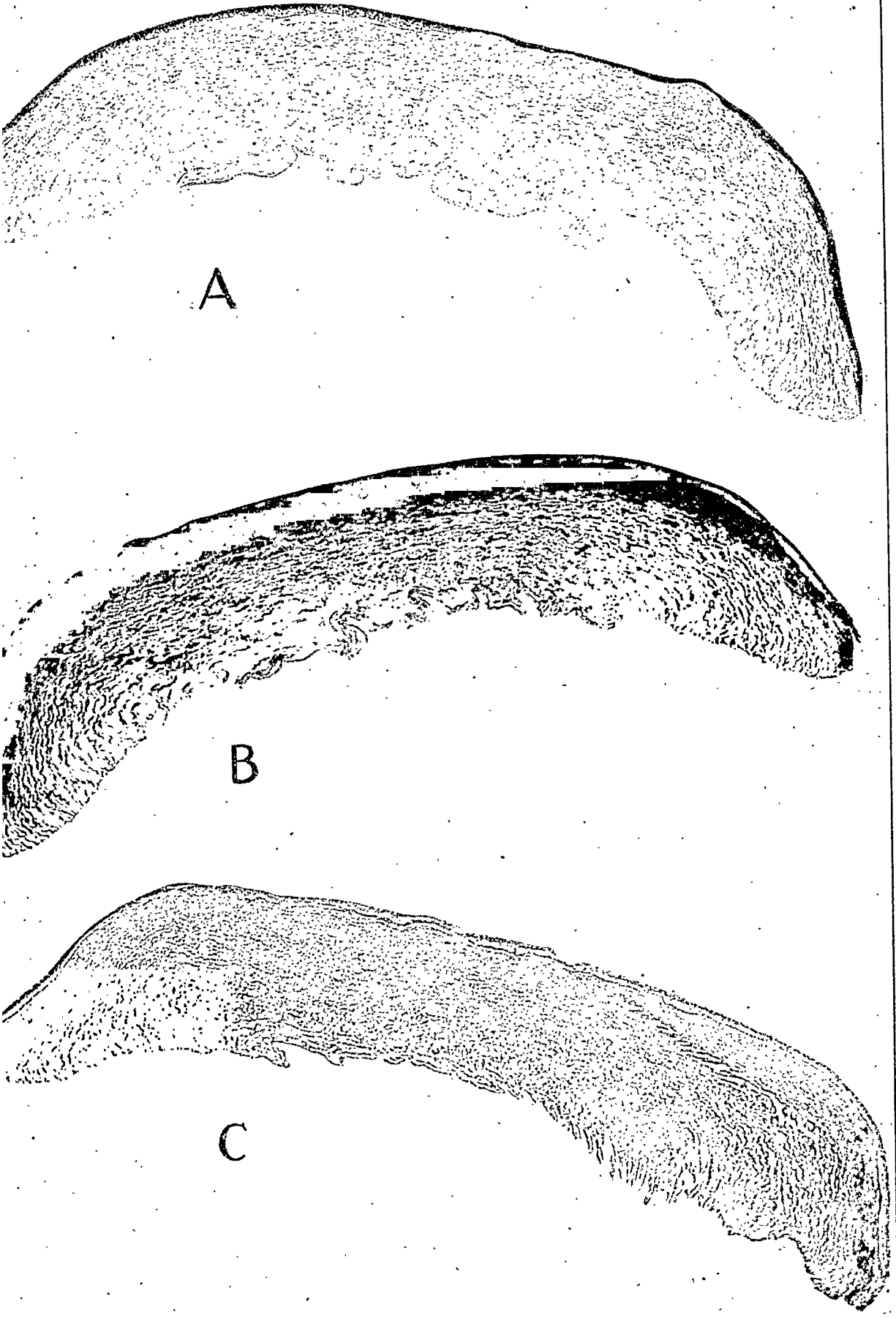


Figure 5

(See legend on opposite page)



third of the corneal stroma. Here and there, bridges of similarly staining epithelium connected the two red layers, leaving islands of blue-staining epithelium isolated from the surface (fig. 6.1a). This peculiar staining pattern was not seen in the slides stained with the Van Gieson method or with hematoxylin and eosin.

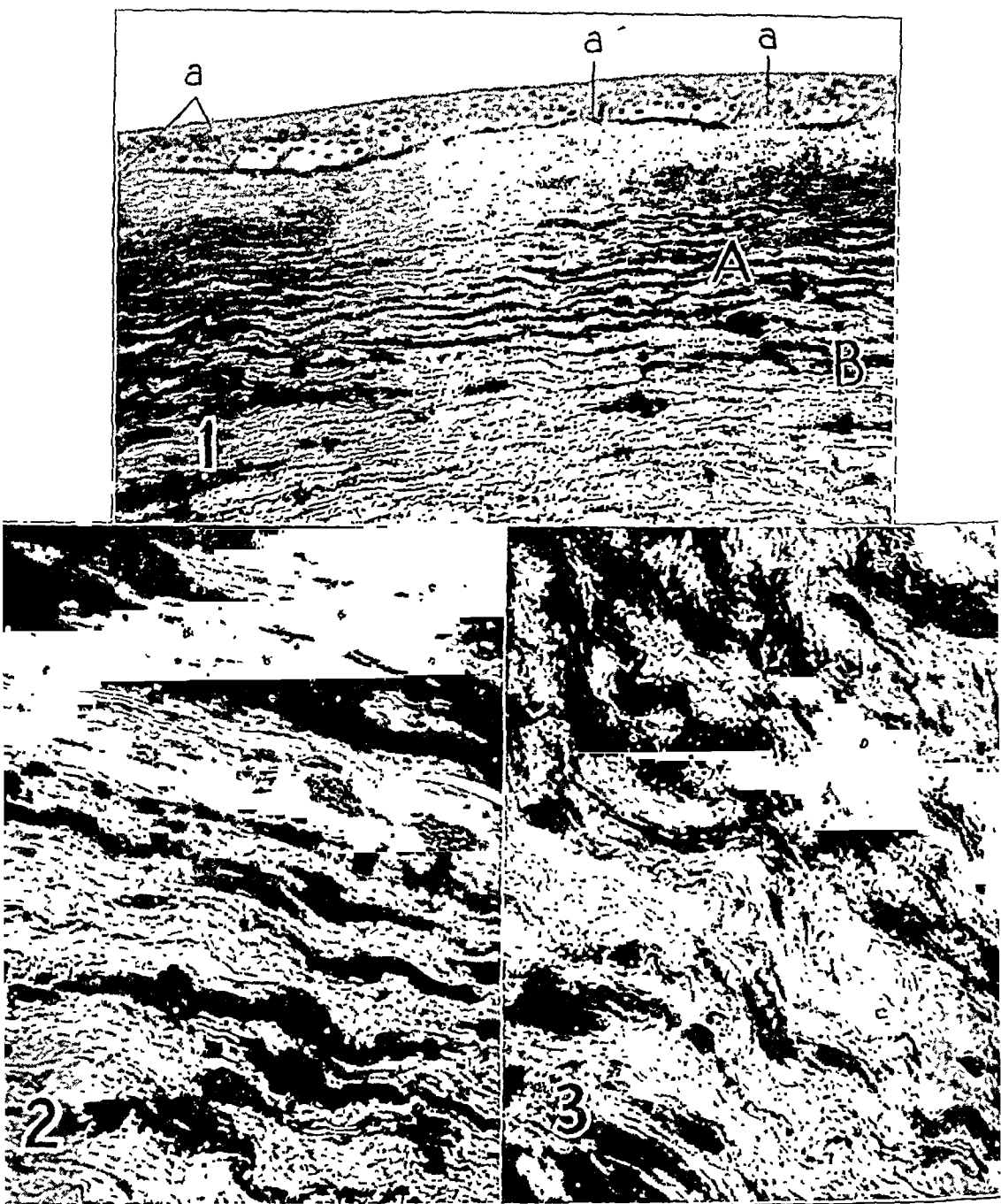


Fig. 6.—Photomicrographs of the sections stained with Masson's trichrome stain. 1, anterior two thirds of this section; a, points to the bridges between the deep-staining anterior part of the epithelium and the stroma. Many of the long, red-staining fibers show up well. 2, a magnification of the stroma at point A in 1, shows the large red fibers and some of the extralamellar deposits; 3, a magnification of the stroma at point B in 1, shows the small intralamellar deposits.

At intervals "bumps," or protuberances, of corneal stroma extended into the epithelium, seeming to push the epithelial cells to each side. These swellings were laminated structures, made up of alternate layers of corneal lamellas and the foreign deposition seen throughout the sections. Figure 7 *A*, a photomicrograph, shows two of the "bumps" from a slide stained with Van Gieson's stain, as well as the alternate red and yellow bands.

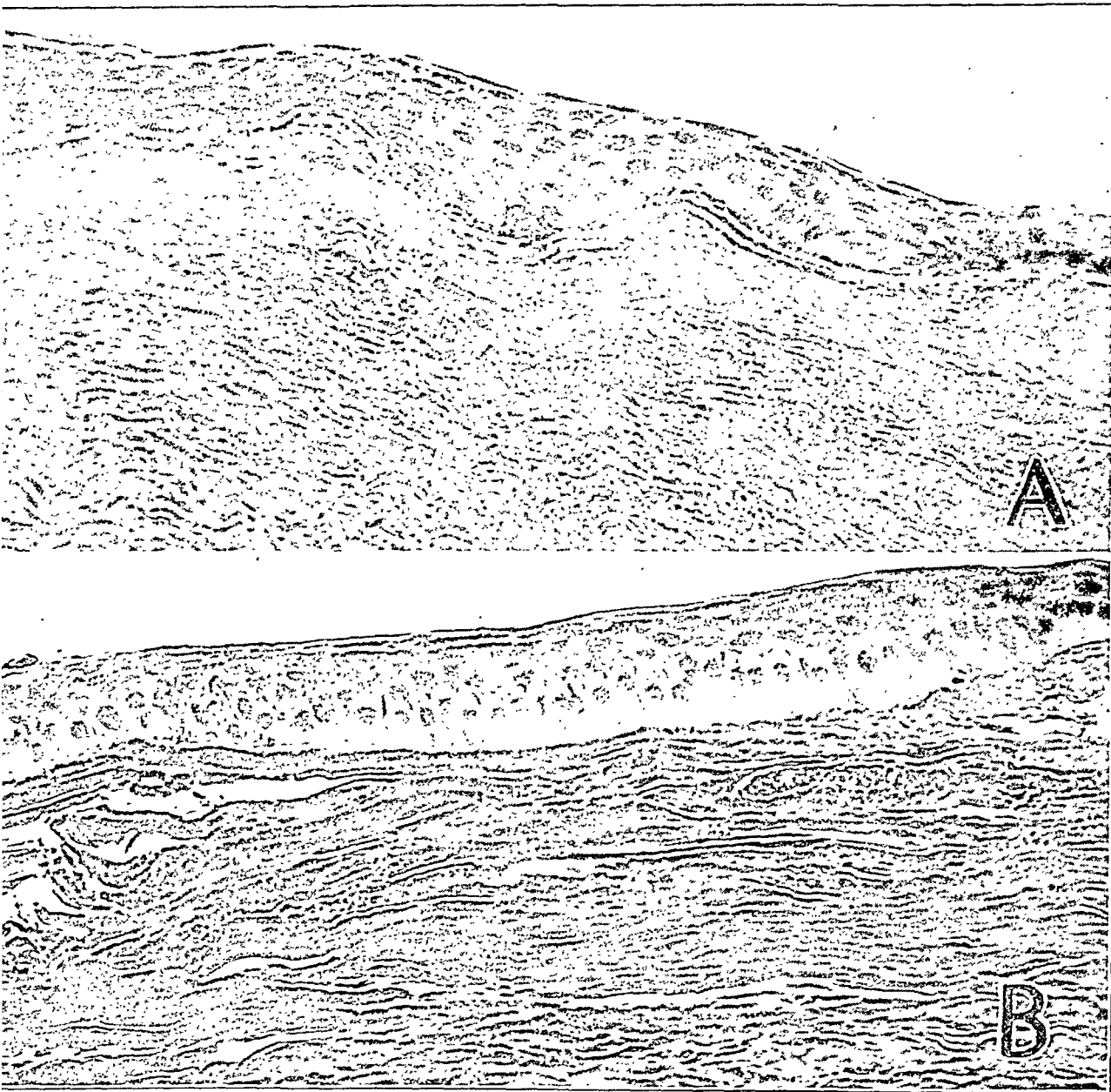


Fig. 7.—Photomicrographs of the sections stained with Van Gieson's stain. *A* shows two of the "bumps" bulging forward into the epithelium, with their laminated structure; *B*, columnar epithelium with superimposed flat, squamous cells and no intermediate layer.

Bowman's membrane could not be seen in any of the sections; at least there was nothing resembling a normal membrane. A line of demarcation could be made out, separating the epithelium from the substantia propria, but it was very irregular and was made of the foreign substance which stained red with the trichrome method and yellow-orange with the Van Gieson method. The irregular-

ities of this line were due not to epithelial downgrowths, but to forward protrusions from the stroma. One received the impression that the stroma was sending forward tongue-like processes into the epithelial layer.

The anterior third of the cornea contained most of the pathologic change. With the trichrome stain, this portion was seen to take a deep red color. It consisted of a dense network of wavy, red bands (fig. 62). In the interstices of this net were seen thin blue bundles, and here and there were islands of blue bundles. The red-staining bands were not homogeneous; they had a fibrillar structure. No nuclei could be seen in the red bands. They appeared to be corneal lamellae but were slightly irregular in their course.

The middle third showed less dense and shorter bands, fewer than in the anterior third, and interspersed with small, irregular patches of the same red substance

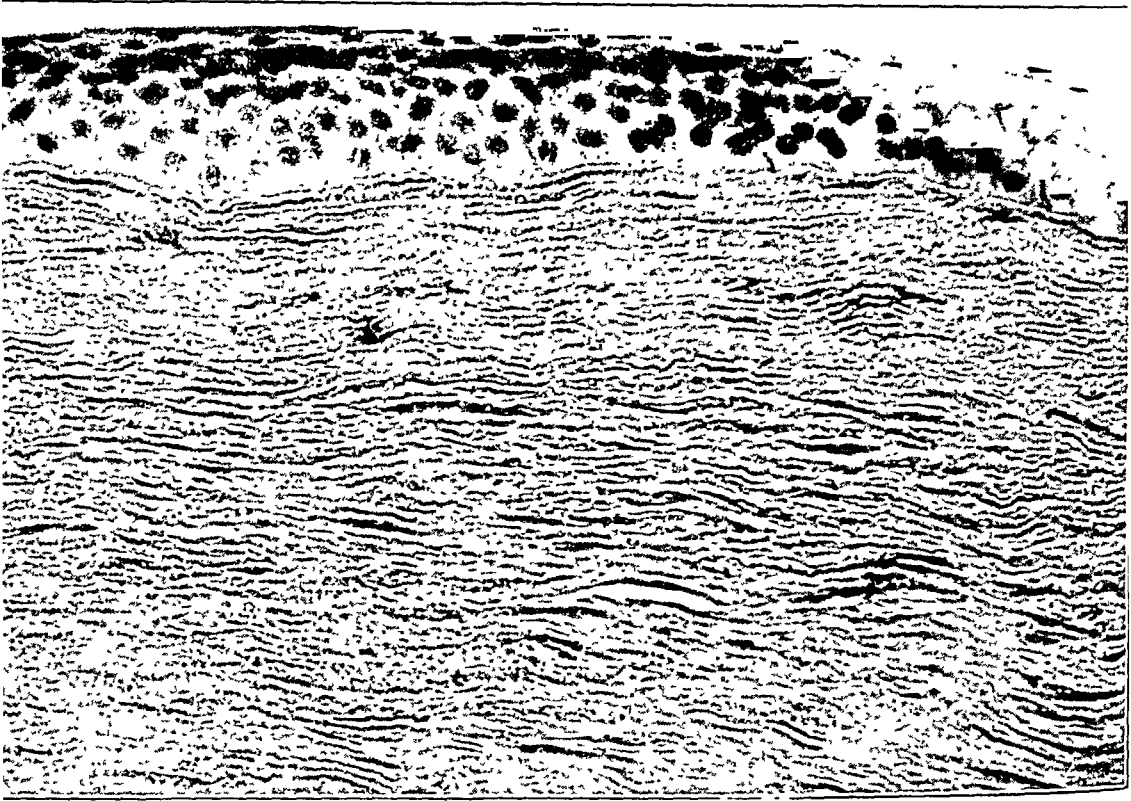


Fig. 8.—Photomicrograph of a section stained with hematoxylin and eosin. Note the apparent scarcity of the abnormal fibers in the anterior third, as compared with the appearance of the trichrome stain.

(fig. 63). These deposits were seen both inside and outside the corneal lamellae. The larger deposits were observed to be extralamellar. The smaller, intralamellar, deposits might number eight to ten or more, were arranged in a row and looked somewhat like peas in a pod. These would seem to represent an earlier stage of degeneration than the solid red lamellae of the anterior third of the stroma. The red deposits were not strictly homogeneous, appearing granular in many places.

The posterior third of the stroma was highly disorganized and wrinkled. It is probable that much of this was artefact, due to shrinking and wrinkling of Descemet's membrane. The same red deposits were found here, but they were even smaller and fewer than in the middle third. They could be found all the way back to Descemet's membrane. No long red fibers were seen in this portion.

Descemet's membrane appeared normal and had retracted into several folds, as it does when incised. The endothelium was bunched in the folds of Descemet's membrane. In some places it stained red in the trichrome sections, contrary to what one would expect. Some of the endothelial cells were larger than normal.

With the Van Gieson stain, the abnormal deposits were seen to take a deep yellow color. Again, the deposits were heaviest in the anterior third, becoming fewer and smaller as one looked posteriorly. Intermingled with the yellow bands were the corneal lamellas, now staining red. With this stain the corneal stroma could be seen to have a dearth of nuclei: in some areas under the epithelium one saw no nuclei at all. In other places, the nuclei were present but stained faintly. Several large, discrete, rounded, yellow deposits could be seen in the anterior half of the stroma, in the interlamellar spaces. The yellow material could also be seen posterior to Descemet's membrane, but with this stain the endothelium looked fairly normal. The outstanding difference between the Van Gieson and the trichrome sections was the fact that the anterior third of the stroma did not show nearly as much yellow deposit with the Van Gieson stain as it did red with the trichrome stain.

The material, so well seen with the trichrome and the Van Gieson stain, was scarcely visible with hematoxylin and eosin. Some granular deposits were seen in the deeper layers (fig. 8). These were pink and hyalin-like. Some areas were devoid of nuclei. There some homogenization of the lamellas in places anteriorly. The "bumps" of stroma protruding into the epithelium could be seen well with this stain.

Frozen sections were prepared and stained with Nile blue sulfate and Sudan III for fat, and with the Schultz stain for cholesterol. All gave negative results. No evidence of fatty degeneration could be found.

CASE 5.—A. D., a white man aged 24, was the son of the patient in case 4. His ocular trouble began in the first six months of life, and during his early years he suffered from attacks of "sore eyes" at approximately monthly intervals. He also went with his father and sisters to certain of the large clinics of the eastern coast.

The patient attended the first four grades of school in the usual manner and stated that he could see fairly well then. Beginning with the fifth grade, however, he attended sight conservation classes and continued to do so throughout the rest of grade and high school. He stated that he was still able to read large print after he had finished high school. He had never worn glasses but had had exotropia as long as he could remember.

During the past few years before he came to the Vanderbilt Clinic, his attacks of "sore eyes" had become less frequent, then occurring only once or twice a year. They had also decreased in severity. Nevertheless, he had noted an increased visual loss in the past four years. When 20 years old, he could still play cards, but he could not do that at the time of examination. Neither could he read any print. He was employed as a pipe fitter and said that he got along satisfactorily at that job. He identified his tools and pipe fittings by touch. He saw well enough with the left eye to get around alone.

The patient's general medical history was essentially noncontributory. He had had two childhood diseases but did not remember which. He broke his arm in an automobile accident when 12 years old. He had had no operations. He had been married for three years and had no children.

*Ophthalmologic Examination.*—The patient was a good-looking, healthy-appearing man, with no visible defect except a divergent squint and the corneal dystrophy.

Vision was perception of hand movements at 2 feet in the right eye and 15/200 in the left eye. Light projection was good in the right eye. Tension was normal in

both eyes. Transillumination revealed nothing abnormal in either eye. The conjunctivas and lids were normal in appearance.

**Corneas:** Macroscopically, there was a gray, grill-like opacity of the cornea in each eye. The opacities presented by this patient were not dense and white in the center, as in the case of his sisters and his father. The pupil and the iris could easily be seen through the opacities, which had the appearance of fine lace. The peripheral clear areas, so distinctive in the other cases, were narrower (about 0.5 mm.) and less distinct in this patient. Corneal sensitivity did not seem to be appreciably decreased, and there was no staining with fluorescein.

Microscopically, with the slit lamp, the lattice-like network was obvious in both eyes. Almost the whole cornea was crisscrossed in every direction with a multitude of fine, gray lines. In the interstices were seen many fine, discrete, round deposits, but no large, conglomerate ones. Although many more lines were found in his corneas than in his sisters' and his father's, the concentration of dots was much less. His condition seemed to be in an intermediate stage between the child's (case 2) and the disease of the other adults. The foreign material was again chiefly located in the anterior portion of the cornea. No blood vessels could be seen. The corneal surfaces were smooth and unbroken by indentations or protuberances. The luster of the epithelium seemed about normal.

The anterior chambers appeared normal in every way. The pupillary reactions were full and equal. The fundi could not be visualized, but a red reflex was present in each eye. He had a divergent squint of about 45 D., with the left eye fixing. Excursions were normal.

**Manifest Refraction:** Vision was not improved with lenses in either eye. It was limited to perception of hand movements at 2 feet in the right eye and to 15/200 in the left eye. There was no further improvement with pinhole disks.

A diagnosis of lattice corneal dystrophy of the Haab-Dimmer type was made. It was felt that the patient had amblyopia ex anopsia in the right eye; in view of that fact, keratoplasty was not recommended for the left eye. He was, however, admitted to the Institute of Ophthalmology for a resection and recession on the right eye for cosmetic purposes. The result was satisfactory cosmetically.

One year later, vision in the left eye was reduced to 3/200 and the patient was having difficulty with his work. On July 7, 1948, a lamellar (nonpenetrating) corneal transplantation was performed on the right eye, and on August 11 a similar operation was done on the left eye. In this procedure the anterior chamber is not incised; a circular disk of corneal tissue is removed from the anterior one half or three quarters of the cornea, and a similar disk is taken from the donor eye and sutured into this defect. Two months later, these grafts were clear, and the patient was able to read the newspaper and telephone book easily (with the left eye, of course). It is too soon, however, to evaluate the result of this procedure.

#### SUMMARY

The lattice type of corneal dystrophy is a chronic, slowly progressive, familial disease of the cornea, inherited dominantly. It begins in the first decade of life, and usually in the first few months. It is characterized in youth by frequent recurrent erosions of the corneal epithelium, associated with severe photophobia, lacrimation and mild conjunctivitis. In the adult years, the recurrent attacks become less frequent and milder, but there is progressive loss of vision. The lesion is always bilateral and occurs as frequently in females as in males. The corneal sensitivity is greatly decreased in advanced cases.

Macroscopically, the corneal lesion is a diffuse opacity, resembling a spider web, involving the whole cornea, except the peripheral 1 or 2 mm. In early cases, interlacing gray lines and fine nodules may be seen with the naked eye or the loupe. Microscopically, the beam of the slit lamp reveals many wandering lines, with a myriad of fine deposits in the interstices, involving all the layers of the cornea, but with a great preponderance in the anterior third. No blood vessels are found in the stroma in uncomplicated cases. Examination of the cornea during one of the "attacks" reveals ulceration of the epithelium over a large mass, or nodule, of the foreign material.

The etiologic factor is unknown. It has been variously suggested that the lesion is due to a nutritional disturbance, a glandular disturbance, tuberculosis, primary degeneration of connective tissues, abiotrophy, degeneration of the corneal nerves or aneurysm of the limbal blood vessels. There is no concrete substantiation for any of these theories.

Pathologically, a hyalin-like material is observed deposited within and without the corneal lamellas and in the epithelium. The intralamellar depositions are tiny and may be found in a row inside the individual fibers. The larger deposits are extralamellar and acquire a considerable size. It is suggested that they are accumulations of the smaller deposits that have broken out of the degenerated corneal fibers. The depositions are concentrated in the anterior layer of the corneal stroma and become progressively fewer toward Descemet's membrane. Bowman's membrane is usually missing. The epithelium is completely disorganized architecturally and is very thin over the large protruding masses in the anterior layers of the stroma.

According to the classification of Bücklers and others, the lattice type of dystrophy is a distinct clinical entity. It is differentiated from the granular type of familial dystrophy by the presence of "lines" in the lesion, by the relatively early loss of vision and by defective corneal sensitivity. It is differentiated from the macular types of corneal dystrophy by the lines and the nodules, its central location in the cornea and its dominant inheritance.

The treatment of corneal dystrophies has always been unsatisfactory. There is no medical agent of any known value. Keratoplasty offers promise at present, but the prognosis is guarded until the permanent outcome of the graft is known.

Approximately 100 cases of this rare disease have been reported in the literature. This report adds 5 cases that fit into the clinical and pathologic pattern of the disease, including that of the youngest patient to be reported up to the present time.

Dr. Gustav Bethke made the drawings with the slit lamp, and Dr. Ludwig von Sallmann aided in the diagnosis and examination of the patients.

704 State Tower Building.

# Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

## Anatomy and Embryology

THE LAMINA CRIBROSA AND ITS NATURE. M. WILCZEK, Brit. J. Ophth. 31: 551 (Sept.) 1947.

Wilczek states that present knowledge of the lamina cribrosa and its function is based mostly on the work of Ernst Fuchs, as there have been no newer researches in this field. In order to be thoroughly acquainted with the structure of the lamina, its relations to the sclera and septums of the optic nerve and its function and importance, Wilczek studied histologic longitudinal and transverse sections of the lamina, not only of adults but of the newborn and embryos and of the cat, pig, horse and ape. His studies demonstrate that the cribriform lamina develops comparatively late and that its complete development is attained as late as the end of fetal life, or even the beginning of extrauterine life. Trabeculae of connective tissue grow into the nerve and the disk from all directions and from all available sources of connective tissue, namely, from the pia mater, from the sclera in the scleral canal and, as can be demonstrated in the series of transverse sections, also from connective tissue which accompanies the central vessels. These connective trabeculae form the septal network of the nerve. By their ingrowth, the nerve is supplied with vessels and its structure strengthened; delicate nervous tissue is connected with the pia mater, and the optic nerve inside the scleral canal is fixed to the sclera.

Wilczek considers fixation of the optic nerve in the scleral canal, i. e., in the place where the optic nerve is exposed to the great danger of being pulled, as one of the most important functions of the cribriform lamina.

He is convinced that there is no substantial difference between the lamina cribrosa and the septal system of connective tissue of the optic nerve. They actually form one common system, the parts of which can be differentiated only by their point of origin. In the scleral canal, trabeculae are thicker because they come from the sclera; in the nerve, they are thinner because they come from the pia mater.

The cribriform lamina is, then, not an independent structure but the foremost and strongest part of the septal system of connective tissue of the nerve. In his studies, Wilczek made a plastic model of the region of the eye, enabling him to visualize the relations in three dimensions.

W. ZENTMAYER.

## Conjunctiva

RECESSION OF LIMBAL CONJUNCTIVA. M. LOMBARDO, Am. J. Ophth. 30: 1109 (Sept.) 1947.

Lombardo suggests recession and permanent fixation of the circumcised margin of the limbal conjunctiva away from the cornea in the cure

of pannus. This results in disappearance of the pannus and permanent improvement of visual conditions, prevents corneal ulcerations and brings about deepening of the fornices.

W. S. REESE.

PRIMARY MENINGOCOCCAL OPHTHALMIA. F. N. SHUTTLEWORTH and J. G. BENSTEAD, *Brit. M. J.* 2: 568 (Oct. 11) 1947.

Two cases of primary meningococcic conjunctivitis in school children in Leeds are described. In 1 case sulfacetimide (*p*-aminobenzene sulfamylacetylimide) was used locally, and in the second penicillin was applied locally, with good results. The importance of recognizing the meningococcus as a primary cause of conjunctivitis is emphasized. The authors note that meningococcic conjunctivitis predominates among males; that in nearly one-half the cases both eyes are involved; that corneal ulceration takes place in one sixth of the cases, but without permanent damage to the eye, and that meningitis is an unusual, but possible, sequel.

ARNOLD KNAPP.

### Congenital Anomalies

TYPES OF CONGENITAL CATARACT. F. C. CORDES, *Am. J. Ophth.* 30: 397 (April) 1947.

In this Sanford R. Gifford Memorial Lecture, Cordes discusses the embryology of the lens and enumerates the various types of congenital cataract; he also reviews the embryology of the vitreous and discusses retrolental fibroplasia and encephalo-ophthalmic dysplasia.

W. S. REESE.

A CASE OF CONGENITAL VERTICAL SHORTNESS OF THE LIDS COMBINED WITH TETRASTICHIASIS. J. LANDAU, *Brit. J. Ophth.* 31: 219 (April) 1947.

A case of congenital shortness of the lids in the vertical direction ("vertical shortness") combined with tetrastichiasis is described. There was a partial eversion of the cutaneous part of the upper lid margin. In spite of an existing lagophthalmos, the eyes remained free from irritation, possibly because of a coexisting hypertrichosis. In the sulcus subtarsalis a dark line was apparent, due to the hair follicles of the supernumerary cilia showing through the conjunctiva. These cilia have probably taken the place of the meibomian glands, occupying their ducts.

W. ZENTMAYER.

PERSISTENCE OF THE HYALOID ARTERY. E. V. BERTOTTO and V. ABREBANEL, *An. argent. de oftal.* 7: 48 (April-June) 1946.

Two cases of persistence of the hyaloid artery are described. In the first case there was also a peripheral area of choroiditis, and in the second case, an area of pigmented choroiditis at the macula. The authors think that there may be a possible connection between the two conditions.

M. E. ALVARO.



## Cornea and Sclera

XEROPHTHALMIA AND KERATOMALACIA IN CHILDREN. A. TUPAS, L. V. PECACHE and A. MELO, J. Philippine M. A. 23:137-190 (April) 1947.

Tupas and his co-workers review observations in 97 cases of vitamin A deficiency with ocular manifestations. Vitamin A deficiency may be brought about in three ways: (1) through inadequate intake of the vitamin; (2) through deficient absorption and storage as a result of intestinal or hepatic derangement, and (3) through an increased demand for the vitamin, as during a period of rapid growth or of disease. In most of the cases observed by the authors, the ocular symptoms were caused by the second and third factors. In several instances admission to the hospital was sought not for the ocular lesion but for dysentery or bronchopneumonia. The ocular lesion, if complained of, was only a minor consideration. Night blindness and photophobia are early symptoms. Examination of the eyes may reveal xerotic conjunctiva and Bitot's spots. Keratomalacia is the advanced form of the ocular lesion due to vitamin A deficiency. It existed in 14 of the 97 cases reviewed. The authors emphasize the importance of early diagnosis and treatment to prevent blindness in infancy and childhood. Treatment consisted mainly in giving foods rich in vitamin A, such as egg, banana and liver. In cases in which the appetite had been impaired or completely lost, vitamin A concentrates and multiple vitamin preparations were given. The local application of vitamin A in oil to the eyes was also tried, with fairly good results.

J. A. M. A. (W. ZENTMAYER).

PHLYCTENULAR KERATOCONJUNCTIVITIS IN A YOUNG GIRL IN RELATION TO THE MENSTRUAL CYCLE. P. BARRAT and A. KOUTSEFF, Bull. Soc. d'opht. de Paris, November-December 1946, p. 100.

A girl aged 14 had recurrence of the lesion two or three days previous to each menstrual period. The reaction to tuberculin was positive locally but negative so far as the ocular or any general reaction was concerned. Therapy with tuberculin was of no avail, but injection of estrogen previous to the expected appearance of the lesion acted as a vaccine. This case is the only one of its type in the authors' experience.

L. L. MAYER.

CURE OF BLINDNESS OF FORTY-TWO YEARS' DURATION BY KERATOPLASTY. ANTONIO TORRES ESTRADA, Bol. Hosp. oftal. Ntra. Sra. de la Luz 3:245 (Jan.-Feb.) 1947.

The case is presented of a man aged 54 in whom lagophthalmos developed in both eyes as a complication of exanthematous typhus. The end result was total loss of vision in the right eye, due to corneal staphyloma, while the patient was able to distinguish only light, colors and, vaguely, very large objects with the left eye. The following year an iridectomy was performed on the left eye at 12 o'clock. The right eye was enucleated because of the staphyloma and recurrent attacks of inflammation. The left eye showed an extensive central adherent leukoma at the lower portion of the cornea, square and surrounded by a transparent zone, through which the iris could be seen. Keratoplasty

was performed, using Castroviejo's technic, and the dressings were removed in fifteen days. The postoperative period was satisfactory. Final visual results were 0.9 for distance and ability to read Jaeger type 1.

M. E. ALVARO.

### Experimental Pathology

#### HISTOLOGIC STUDY OF EXPERIMENTAL CORNEAL TRANSPLANTATION.

H. M. KATZIN and P. K. KUO, *Am. J. Ophth.* 31: 171 (Feb.) 1948.

Katzin and Kuo summarize the literature on the histology of corneal transplantation, both human and experimental, and discuss the evidence in favor of true healing versus replacement of the graft.

Their experimental studies are presented, with sections showing normal healing as well as operative complications. Since corneal tissue is unique in its properties of transplantability, considerable emphasis is placed on this phase.

The authors believe that, in successful cases, the cellular elements of the transplant are replaced by the host, and that the intercellular structures of the graft are accepted and persist.

W. S. REESE.

### General

#### AN OCULIST IN SWITZERLAND. J. FOSTER, *Brit. J. Ophth.* 33: 83 (Feb.) 1948.

This is an interesting and informative account of the author's visit to the ophthalmic clinic at Basel, Schaffhausen, Zurich, Berne, Lausanne and Geneva. It contains a description of the newer methods of examination, operations and apparatus employed in the various clinics. The article does not lend itself to abstraction.

W. ZENTMAYER.

#### OCULAR ALLERGY. C. PAVIA, *Rev. brasil. de oftal.* 5: 29 (Sept.) 1946.

The author presents 2 cases of ocular allergy. The first case was that of a man aged 60 who had been operated on for senile cataract. The operation and the postoperative period were uneventful. Drugs used before, during and after operation were cocaine, merbromin, procaine hydrochloride, physostigmine and atropine. A month later the second eye was operated on, and the procedure was interrupted several times, owing to the condition of the patient, who was perspiring profusely, with slow pulse and dyspnea, these symptoms having commenced after the retrobulbar injection of procaine. Allergy being suspected, 0.5 cc. of procaine hydrochloride was injected intradermally, causing development of the same symptoms. The second case was that of a man aged 21, with acute catarrhal conjunctivitis. No results were obtained with the classic therapy. Treatment was suspended for two days, and at the end of this period the allergic symptoms disappeared. Cocaine was suspected as the allergin.

M. E. ALVARO.

### General Diseases

#### ARACHNODACTYLY (MARFAN'S SYNDROME) ASSOCIATED WITH ECTOPIA LENTIS. J. V. CASSADY and C. B. MCFARLAND, *Am. J. Ophth.* 30: 469 (April) 1947.

Cassady and McFarland review the literature of Marfan's syndrome, emphasizing its hereditary and familial tendencies. They report a case with the usual characteristics, as well as a detached retina pulled loose by a dislocated lens and a pigmented, band-shaped corneal degeneration. The lens was removed, but vision was limited to light perception and projection. The fellow eye was blind from glaucoma.

W. S. REESE.

EXTENSIVE SYMMETRICAL CEREBRAL CALCIFICATION AND CHORIORETINITIS IN IDENTICAL TWINS (TOXOPLASMOSES?). K. H. ABBOTT and J. D. CAMP, *Bull. Los Angeles Neurol. Soc.* 12: 38 (March) 1947.

Abbott and Camp report observations on twin boys aged 11 years who were brought to the Mayo Clinic because of visual disturbances and disturbances of movement in the right extremities. The disturbances were more evident in the more severely affected of the two boys, who also had bilaterally symmetric, extensive, dense calcification in the cerebrum with minor involvement of the cerebellum. Both patients had extensive chorioretinitis, which was severer on one side, associated with retinal angiomas. Blood serum from each twin neutralized toxoplasma organisms. The pathogenesis and the histopathology of this syndrome—symmetric cerebral calcification, chorioretinitis with retinal angiomas and toxoplasmosis—are unknown. Although a degenerative process occurring in symmetric anomalies of vascular or heterotopic nervous tissue or both may be the causal factor, it is more plausible that the syndrome is due to an inflammatory process, probably consequent to chronic toxoplasmosis.

W. ZENTMAYER.

THE FUNDUS IN CASES OF HYPERTENSION IN WHICH THE SMITHWICK METHOD WAS USED. M. PUIG SOLANES, *Gac. méd. de México* 77: 16 (Feb.) 1947.

The author reaches the following conclusions:

1. During the first few weeks after the Smithwick operation in cases of hypertension, an increase in the narrowing of the retinal arterioles, which accentuates the "edematous" papilloretinal lesions, is observed.

2. Within a few months the angiospasm (localized constrictions) and the "edematous" lesions disappear, the tonic contraction (generalized uniform narrowing) of the arterioles remaining. These, according to investigators who have kept the patients under observation for years after operation, also tend to disappear in time.

3. The alterations in the retinal vessels in the patients after operation are independent of the effect produced by the operation on the arterial tension and the general health of the patient.

4. It is supposed that similar alterations occur in other circulatory regions of the organism, especially in the brain. M. E. ALVARO.

### General Pathology

DATA ON THE OCCURRENCE OF CALCIFICATION IN THE EYE TISSUES. M. RADNÓT, *Brit. J. Ophth.* 32: 47 (Jan.) 1948.

The cases discussed in this study were those of so-called ribbon type degeneration. It was sought to find out what changes are present

in tissues of the eye other than the cornea, especially whether calcareous deposits occurred elsewhere. On the basis of this investigation, it is observed that when lime is deposited in the cornea in zonular opacity or in eyes injured in some other way, a calcareous deposit is also to be seen in other tissues of the eyeball. The article is well illustrated.

W. ZENTMAYER.

### Glaucoma

ACUTE GLAUCOMA: A FOLLOW-UP STUDY. H. S. SUGAR, *Am. J. Ophth.* 30: 451 (April) 1947.

From a study of 45 patients with "primary" acute glaucoma followed over a period of six years, Sugar concludes that the inclusion of a description of the vascular reaction of the eye in the main diagnosis is unjustified, the various types of response constituting clinical phases of the same condition. He also concludes that miotics have the disadvantage of adding a congestive, angle-narrowing factor in a situation in which the angle is already anatomically too narrow. He suggests the use of a combination of miotics and vasoconstrictors.

W. S. REESE.

INDICATIONS FOR IRIDECTOMY IN HEMICYCLODIALYSIS. ANTONIO TORRES ESTRADA, *Bol. Hosp. oftal. Ntra. Sra. de la Luz* 3: 237 (Jan.-Feb.) 1947.

The author believes that iridectomy is a valuable aid in hemicyclocaldialysis, making the latter operation less dangerous and eliminating its complications. Iridectomy may be performed weeks before the hemicyclocaldialysis, or at the same operative session.

Iridectomy should be mandatory as the final stage of the operation in cases of hemorrhage and when abundant segregation of uveal pigment is present. Iridectomy combined with hemicyclocaldialysis is also indicated in cases of a shallow anterior chamber, in the slightly advanced stages of glaucoma, in cases of congestive glaucoma, in cases with degenerative lesions of the iris and in cases in which the general condition of the patient allows one to foresee inflammatory reactions during the post-operative period.

M. E. ALVARO.

### Hygiene, Sociology, Education and History

OPHTHALMOLOGY DURING THE WAR AND IN THE FUTURE. S. DUKE-ELDER, *Am. J. Ophth.* 30: 1073 (Sept.) 1947.

In this address, presented at the eighty-second annual meeting of the American Ophthalmological Society, the author considers advances in chemotherapy, various aspects of physiology, evaluation of experimental opportunities, integration of research and responsibilities of the future.

W. S. REESE.

NEW YORK AS AN OPHTHALMOLOGICAL CENTER. B. SAMUELS, *Am. J. Ophth.* 30: 1081 (Sept.) 1947.

This interesting account begins with the founding of the New York Eye Infirmary in 1820, around which revolved all matters concerned

with the eye. Outstanding ophthalmologists and various ophthalmologic institutions are mentioned as they fit into this history.

W. S. REESE.

### Injuries

TREATMENT OF TRAUMATIC DIPLOPIA. J. C. NEELY, Brit. J. Ophth. 31: 581 (Oct.) 1947.

The material for this lengthy dissertation was drawn from the records of patients who were seen by Neely at a military hospital for head injuries and at a Royal Air Force hospital. A complete analysis of each of the 55 cases is appended.

The following summary is given:

1. Traumatic diplopia is not an uncommon sequel to a head injury.
2. Diplopia is caused usually by a paresis, and not a paralysis, of an extraocular muscle.
3. In the majority of cases, the "closed" head injury, and not the penetrating head wound, is the cause of diplopia.
4. The vertically acting muscles are most often affected.
5. Injuries to the orbit tend to be overlooked, owing to the severity of other injuries, or masked by the swelling of the surrounding tissues.
6. The roentgenologic diagnosis of fracture of the floor of the orbit is difficult to make unless stereoscopic pictures are taken in the vertical position of the head.
7. In cases of fractures involving the orbit, the restoration of the normal anatomic relation of the parts is of immediate importance.
8. The orbital floor can be built up by means of a bone inlay if immediate restoration has not been effected.
9. Well planned surgical procedures on the extraocular muscles, aided by orthoptic exercises, represent the best means of overcoming the residual diplopia and of restoring binocular single vision.

The article is illustrated with photographs of the patients' eyes in the fields of fixation, charts of the field of fixation and, in many cases, roentgenograms of the orbit and skull.

W. ZENTMAYER.

### Lens

THE ACTION OF SULPHANILAMIDE ON RABBITS' LENSES IN VITRO. A. BAKKER, Brit. J. Ophth. 31: 216 (April) 1947.

The perfusion culture method gave reliable information on the toxic action of chemicals. The present experiments showed that sulfanilamide has no injurious effect on rabbit lenses when the concentration is not raised above the level reached in normal therapeutic doses. Nevertheless, caution is advisable in using this drug. The author was told that in a 43 year old patient, with erysipelas of the face, who was treated with "prontosil" (the hydrochloride of 2,4-diaminoazobenzene-4-sulfonamide) for no less than four months there developed cataractous changes of capsular and subcapsular type in both lenses.

There was a striking difference between the behavior of the lenses of young and those of old animals. The younger the animals, the more their lenses were susceptible to the noxious influence of sulfanilamide.

W. ZENTMAYER.

CATARACT AFTER TETANY. R. GARCIA OCHOA and A. ETCHEMEN-DIGARAY, *An. argent. de oftal.* 7:7 (Jan.-March) 1946.

Tetany is not frequent, and cataract as a complication of tetany is even less so. A woman aged 41 had been treated for hyperthyroidism for three years, and at the end of this time the lower portion of the right thyroid gland was removed. On the third postoperative day an acute attack of tetany occurred, for which intravenous injections of calcium were given. Since the attacks continued as soon as injections were suspended, a graft of parathyroid tissue on each side of the trachea was performed. The tetany continued until four more grafts had been made. Thirteen months after the first symptoms of tetany, total, bilateral cataract, obviously correlated with the tetany, was noted. The pathogenesis of such cataracts is discussed. M. E. ALVARO.

### Methods of Examination

MEASUREMENT OF RELATIVE EXOPHTHALMOS BY ROENTGENOGRAPHY.

BENJAMIN FRIEDMAN, *U. S. Nav. M. Bull.* 45:482 (Sept.) 1945.

The patient lies on the x-ray table, with eyes looking straight upward; a contact glass carrying a small central lead dot is placed over each eye; the roentgen rays are directed from the foot of the table so that the central ray passes through the lead dots at an angle of 35 degrees with the table; the shadows of the lead dots fall on the film. If one eye protrudes more than the other, the dot over the relatively exophthalmic eye will be projected farther back than the dot over the less protruding eye. A method of positioning the eyes in space in such a manner as to eliminate sources of error is described. The measurements are precise and are in most cases less than the variations found in repeated readings with the exophthalmometer. They record relative, not absolute, exophthalmos. This method does not supplant instrumental exophthalmometry; the two methods should supplement and check each other.

BENJAMIN FRIEDMAN.

PERIMETRIC CHARTS IN EQUIVALENT PROJECTION, ALLOWING A PLANOMETRIC DETERMINATION OF THE EXTENSION OF THE VISUAL FIELD. J. TEN DOESSCHATE, *Ophthalmologica* 113:257 (May) 1947.

In this study, the author attempts to project the visual field as recorded from the surface of a sphere on to a plane surface, that is, a perimetric chart. The problem is the same as that which has been studied for centuries by geographers and astronomers. The author discusses problems involved in detail and describes a perimetric chart in equivalent projection which allows a planometric determination of the area of the field of vision on the visual sphere. If  $C$  represents the relative part of the visual field (and of the retinal surface approximately) which is still physiologically active, then  $C$  equals

$$\frac{S}{S_0}$$

where  $S$  represents the surface of the visual field of the patient and  $S_0$  is the surface of the normal visual field. The author attempts, further, to describe the construction of a perimetric chart in which the area of the field is a measure of the active number of percipient retinal units. It is shown, however, that such a chart has no practical clinical value.

F. H. ADLER.

## Neurology

DISEASES OF THE BRAIN AND OPTIC NERVE: CONCENTRIC RESTRICTION OF VISION FROM UNILATERAL CEREBRAL LESIONS. A. PATERSON, Tr. Ophth. Soc. U. Kingdom 64: 115, 1944.

Concentric constriction of peripheral vision in the nonhemianopic half-fields arising from a unilateral lesion has frequently been observed in the past. Although the older neurologists believed that this syndrome had an organic basis, it is now usually considered to be of functional origin. Two cases presenting these field changes are reported. In both, sustained fixation was difficult. In the first case the patient sustained a unilateral tangential, through and through bullet wound; the entrance was in the right frontal region and the exit just in front of the tip of the right ear. As a result, there was a large intracerebral hemorrhage in the right cerebral hemisphere from rupture of a branch of the middle cerebral artery, giving rise to left hemianesthesia and hemiplegia. In the second case the diagnosis was that of cerebral thrombosis, either in a terminal branch of the middle cerebral artery in the region of the angular gyrus, and affecting in the main the optic radiation in its narrow part as it sweeps round the temporal horn, or, more probably, in the posterior cerebral artery, fairly far forward and affecting the subcortical connection of the angular gyrus. An explanation of these field changes is attempted. One factor may be the difficulty in sustained fixation. Two possible factors in this phenomenon are, first, a probable defect in oculomotor integration and, second, impairment of the visual attention process itself. Another factor may be that the test object fails to excite attention, or at least to evoke a perceptual response, until it approaches the region of central vision. Still another factor is dark adaptation, which was poor in both cases, as the luminosity of neither test object nor background is as a rule particularly high and some degree of dark adaptation almost certainly takes place during the test. The discrepancies between the results of perimetric and campimetric examinations are described: The fields are much more constricted on the screen than on the perimeter; this may be interpreted as a gross exaggeration of a normal phenomenon, namely, that peripheral acuity is better for a near object than for a distant one when both are arranged to subtend identical retinal angles and the illumination is likewise equated.

W. ZENTMAYER.

THE CENTRAL VISUAL FIELD AFTER OCCIPITAL LOBECTOMY. K. PORSAA, *Acta ophth.* 22: 241, 1944.

The theory of bilateral macular representation in the cortex has been questioned by many investigators. One of the chief arguments against it is the frequent occurrence of occipital hemianopsias without macular sparing—a fact which any acceptable theory must take into account. Horrax and Putnam, for instance, found macular sparing in only 74 per cent of cases of hemianopsia resulting from uncomplicated occipital tumors, and Allen, in 39 per cent.

After a brief consideration of other theories that have been advanced to explain sparing of the macula, the author reports 5 cases in which

an occipital lobectomy was performed without injury to the corpus callosum or involvement of the temporal lobe. The fields of vision in all 5 cases were taken after the patient had staged a good recovery. In all cases there was a sharply defined hemianopsia with bisection of the macula. The author believes that these cases show more clearly than any previous investigative studies that there can be no bilateral representation of the macula in the cortex.

O. P. PERKINS.

### Ocular Muscles

TESTS FOR HETEROPHORIA. R. G. SCOBEE and E. L. GREEN, *Am. J. Ophth.* 30:436 (April) 1947.

Scobee and Green conclude from tests on the eyes of cadets of the air corps that Maddox rod tests give results sufficiently like those with the screen and parallax test to be used as a routine. They recommend that a white rod be used, without screening, and that it may be placed before the dominant or the nondominant eye, according to routine.

W. S. REESE.

SOME OBSERVATIONS ON THE SURGICAL TREATMENT OF THE EXTRA-OCULAR MUSCLES. A. DEH. PRANGEN, *Am. J. Ophth.* 30:1161 (Sept.) 1947.

Prangen expresses his individual views on surgical treatment of the extraocular muscles and refers to his technic in and preference for various operative procedures.

W. S. REESE.

ORTHOPTIC TREATMENT IN CONVERGENCE INSUFFICIENCY. C. E. DAVIES, *Canad. M. A. J.* 55:47, 1946.

Davies has found that convergence insufficiency bears no relation to refraction and is not cured by correction of refractive errors, except in some cases of undercorrected myopia and overcorrected hypermetropia. The incorporation of prisms in a prescription will not constitute a cure, as prisms do not produce the development of a convergence reserve. In the author's experience, operation has not proved satisfactory in cases of convergence insufficiency, as the condition is functional. In extreme cases, however, it may go on to heterophoria. Repeated convergence on a test object is a quick and accurate test for convergence insufficiency. Convergence insufficiency with esophoria was found to take the longest time to correct because correct abduction had to be taught as well as adduction, i. e., divergence insufficiency.

W. ZENTMAYER.

### Operations

USE OF DEAD TISSUE IN OPHTHALMIC REPAIR. A. MAGITOT, *Ann. d'ocul.* 180:146 (March) 1947.

The author discusses the use of both living and preserved tissue as transplant material in the human body. In most instances the donor material is replaced by cells from the host.



Reference is made to the use of calf's cartilage and its perichondrium for implantation in Tenon's capsule after enucleation. Recently the author has used the head of the femur from a dog. It is stripped of all cartilage and then preserved in 60 per cent alcohol. After operation there is the minimum reaction to the transplant. With the availability of such material, there is no reason for using inert implants in the socket. One should also pay attention to the cosmetic appearance of the patient. The sunken upper lid can be improved by placing a suitable plastic or cartilage in the upper lid under the brow.

P. R. McDONALD.

USE OF THROMBIN-GELATIN SPONGES IN OPHTHALMIC SURGERY.  
CRUT and A. DOLLFUS, Bull. Soc. d'opht. de Paris, March-April 1947, p. 126.

The authors used thrombin-gelatin sponges in 4 cases of surgical procedures for ocular conditions, viz., staphyloma of the cornea, painful absolute glaucoma with trophic keratitis, exenteration of the orbit and painful absolute glaucoma with thrombosis of the central retinal vein. In all cases the bleeding was stopped very quickly. The length of the duration of each operation was definitely shortened. It is necessary to follow the recommended technic for best results in the use of this new method of controlling bleeding.

L. L. MAYER.

### Orbit, Eyeball and Accessory Sinuses

THE ROLE OF THE DIENCEPHALON IN REGULATING OCULAR TENSION.  
E. SCHMERL and B. STEINBERG, Am. J. Ophth. 31:155 (Feb.) 1948.

Schmerl and Steinberg conclude that it may be postulated, on the basis of experiments performed under the conditions described, that the diencephalon contains a center or centers which exercise a regulating control of ocular tension. The experiments also suggest an instability of the diencephalic center or centers in glaucomatous animals.

W. S. REESE.

NONINFLAMMATORY EXOPHTHALMOS. ESTEBEN ADROGUE and FEDER-AICO C. CERBONI, Arch. de oftal. de Buenos Aires 23:1 (Jan.-March) 1947.

The authors discuss exophthalmias of the noninflammatory types.

*Definition.*—Exophthalmos means a displacement of the eye forward, out of the normal anatomic position it occupies in the orbit. Anatomic and physiologic details are given.

*Pathogenesis.*—The pathogenic factors are: (1) a decrease in the forces which maintain the globe in its position in the orbit, (2) an increase in the quantity of blood in the orbit and (3) an increase of the orbital contents, due to neoplasms.

*Semeiologic Considerations.*—The authors classify the various types of exophthalmos on the basis of the following factors: direction; evolution; reducibility; involvement of motility; palpability and nonpalpa-

bility; alterations in the fundus, vision or visual fields; associated local symptoms; roentgenographic symptoms; diagnostic proof, and general clinical data, such as age, frequency, sex and localization.

*Therapy.*—The treatment of noninflammatory exophthalmos depends on the cause and is usually surgical; therefore, only the types which respond to surgical treatment are considered in this article. Various types of operations are discussed.

M. E. ALVARO.

### Retina and Optic Nerve

PAPILLEDEMA AND PAPILLITIS. M. CHAMLIN, *Am. J. Ophth.* 30:741 (June) 1947.

Chamlin discusses papilledema and papillitis from the standpoint of ophthalmoscopic findings, visual acuity and visual fields. He concludes that studies of the central fields are of paramount importance in the differentiation of these two conditions.

W. S. REESE.

EXPERIMENTAL STUDIES IN RETROBULBAR NEURITIS. P. J. LEINFELDER and W. A. ROBBIE, *Am. J. Ophth.* 30:1135 (Sept.) 1947.

Despite the fact that the groups of animals with deficiencies in B complex and in thiamine were reduced to extreme degrees of malnutrition, in none of their experiments did Leinfelder and Robbie find significant degeneration in the optic nerves. They discuss the results of these experiments in their significance and mention certain inadequacies of the present experimental methods.

W. S. REESE.

RETINAL HEMORRHAGES PRECEDING PAPILLEDEMA. G. OFFRET, *Bull. Soc. d'ophth. de Paris*, November-December 1946, p. 65.

Attention to retinal hemorrhages, in 2 patients with vasomotor reactions, is focused on the development of papilledema. Both patients had intracranial lesions, and the author believes that the retinal hemorrhages are an early phase in the development of edema of the nerve head.

L. L. MAYER.

HOLE IN THE MACULA AFTER A SINGLE HEMORRHAGE. A. B. RECA, *An. argent. de oftal.* 7:10 (Jan.-March) 1946.

A woman aged 29 years complained of a sudden decrease in visual acuity in the left eye. The optic disk appeared to be normal; the arteries were thin and somewhat rigid. Along the course of the large veins small hemorrhages were visible. A large hemorrhage occupied the entire region of the macula. Twenty days after the first examination the hemorrhage had disappeared, leaving in its place an oval hole. The bottom of the depression was brownish, with large, brilliant dots, possibly due to cellular disintegration. The author reaches the following conclusion: Owing to the absence of a history of earlier ocular disease, the brownish color of the lesion and the presence of the large, brilliant spots, as well as the permanent character of the lesion, the lesion may be classified as a "traumatic hole of the macula."

M. E. ALVARO.

MIGRATING CILIARY NODULES ON THE RETINA. D. DÍAZ DOMINGUEZ, Arch. Soc. oftal. hispano-am. 6: 265 (March) 1946.

Díaz Dominguez describes his observations in the case of a woman aged 62 who presented signs of bilateral iridocyclitis. There were ciliary injection and pain on pressure in both eyes. Examination revealed keratic precipitates on Descemet's membrane and pigmented deposits on the anterior surface of both crystalline lenses and floating cells in the vitreous. The fundi were normal on the first examination. Four days later, however, the author observed in the lower part of each fundus, toward the periphery, two small, whitish, prominent spots, which he interpreted as two foci of choroiditis. The patient felt better under treatment and disappeared, to come back two years later with recurrence of symptoms. This time the author observed two new nodules in the lowermost part of the fundus in the right eye, in the vicinity of those seen two years before. This time he could see that the well limited, grayish white nodules were located on the surface of the retina. Because of their location on the retina, and in the most dependent portion of the fundus, the observer concluded that these formations had dropped off from the ciliary body, to be lodged in the retina.

Similar cases had been described before by Szily and Krückmann, but the author is not in accord with Szily in his assertion that the condition occurs only with tuberculous iridocyclitis. He is of the belief that, as in his case, in which the condition was proved not to be tuberculous, these migrating nodules may be associated with any type of anterior uveitis.

H. F. CARRASQUILLO.

### Tumors

CANCER OF EYELID TREATED BY RADIATION, WITH CONSIDERATION OF IRRADIATION CATARACT. H. B. HUNT, Am. J. Roentgenol. 57: 160 (Feb.) 1947.

The survey presented by Hunt is based on a study of 100 cases selected from 134 occurring from 1930 to 1946. Carcinoma of the eyelid is a disease of the older age group, three fourths of the patients being past 60 years of age. Men are slightly more susceptible than women. Four fifths of the lesions are located along the lower lid or about the inner canthus. Basal cell carcinoma represents three fourths of the neoplasms of the eyelid, and this lesion is usually of slow growth. Squamous cell carcinoma of the eyelid, although not common, is a more serious lesion, shows greater local invasion and frequently metastasizes to the parotid or the submaxillary gland. Cancer of the eyelid can be as effectively controlled by fractionated roentgen therapy as by surface application of radium. Careful fulguration is the treatment of choice in the removal of benign moles or papillomas. Surgical ablation of a large, elevated carcinoma of the eyelid prior to roentgen therapy permits more effective treatment of its base, with less mass irradiation of the eyeball and other adjacent, nondiseased, tissues by both primary and scattered rays. In 4 of the 100 cases reviewed, death occurred from cancer of the eyelid during the past fifteen years. Therapeutic failures are the result of advanced and inaccessible disease, impairment of the tumor bed by prior inadequate therapy, insufficient or uneven dosage, incomplete marginal coverage of the lesion and inadequate follow-up observation of the patient. Superficial roentgen therapy is effective in

eradication of cancer of the eyelid, with maximal preservation of the uninvolved tissues and with minimal injury to the eye when properly protected by an eye shield.

J. A. M. A. (W. ZENTMAYER).

MALIGNANT RETICULAR TUMORS OF THE FACE. J. DELARNE and G. OFFRET, Bull. Soc. d'opht. de Paris, November-December 1946, p. 103.

Deep tumors of the face as noted by the clinician are epitheliomas of the bony cavities and osseous sarcomas.

Tumors were observed in the orbit in 10 cases; in the nasal fossa, in 1 case; in the inferior maxilla, in 2 cases; in the frontomalar region, in 1 case, and in the superior maxilla, in 1 case.

The authors divide the reticular tumors as follows: (1) indifferent reticulosarcoma, (2) reticuloangioendotheliosarcoma and (3) lymphoreticulosarcoma.

The authors discuss the various tumors in respect to age of appearance, type and relation to other disease processes, such as mycosis fungoides, either local or general. They believe that the Mikulicz tumor is a separate entity.

L. L. MAYER.

SPONTANEOUS CYST OF THE IRIS. H. MARBACK, Arq. brasil. de oftal. 9: 1 (Feb.) 1946.

A woman aged 27 complained of a small spot on the iris of the right eye. This spot had not increased in size or changed color. There was no history of trauma. Examination revealed a small tumor in the upper temporal quadrant of the iris, and in the anterior chamber there was a small cyst between the anterior surface of the iris and the posterior surface of the cornea. Surgical removal of the cyst was recommended, but permission was refused by the patient. Examination made two and a half years later showed no change in the size of the cyst.

M. E. ALVARO.

CHOROID METASTASES IN CHORIONEPITHELIOMA [CHORIONIC CARCINOMA] OF THE TESTICLE. E. GODTFREDSSEN, Acta ophth. 22: 300, 1944.

In a youth aged 18, a tumor of the right testis necessitated semi-castration. Microscopic examination of the growth revealed chorionic carcinoma. Shortly after the operation, choroidal, cerebral and pulmonary metastases occurred, ending in the patient's death twelve months after the onset of symptoms. All the metastatic growths were of the same type as the original tumor.

O. P. PERKINS.

ON THE FREQUENCY OF SECONDARY CARCINOMAS IN THE CHOROID. E. GODTFREDSSEN, Acta ophth. 22: 394, 1944.

In a series of about 8,000 patients with cancer attending the radium center and the Finsen Institute, in Copenhagen, choroidal metastases developed in 6. Such metastases occur with equal frequency with pulmonary cancer and with cancer of the breast. Furthermore, metastatic tumors constitute between one third and one half of the total number of intraocular tumors occurring in Denmark.

O. P. PERKINS.

## Uvea

THE INFLUENCE OF HYPERSENSITIVITY ON ENDOGENOUS UVEAL DISEASE. A. C. WOODS, *Am. J. Ophth.* 30: 257 (March) 1947.

In this, the Jackson Memorial Lecture, Woods discusses the influence of hypersensitivity on endogenous uveal disease. The clinical difference between two types of uveal disease, nongranulomatous and granulomatous, are pointed out. Both types are dependent on invasion of the eye, at one time or another, by living bacteria; but the pathogenesis and character of the lesions in these two types of uveal disease appear to be quite different. In the nongranulomatous type, the primary invasion of the eye is probably by organisms either of low virulence or in small numbers. The result is that they are destroyed by the normal bactericidal action of the ocular fluids. This primary invasion produces insignificant lesions or no lesions at all, but it does produce a local hypersensitivity of the ocular tissues to the bacterial protein or to the soluble bacterial products. This hypersensitivity may be of the bacterial type, or of both the anaphylactic and the bacterial type. When the bacterial antigens again reach the eye, either through reinfection or absorption from an infected focus, or even a normal cutaneous surface or mucous membrane, there results a hypersensitive reaction in the eye. This reaction is produced either by organisms which do not proliferate or by their bacterial products. In either event, the reaction is essentially an evanescent one and is characterized by an intense vascular congestion and a minimum of tissue damage—the picture of a nongranulomatous uveitis.

In the granulomatous type of uveitis, the mechanism is quite different. The organisms reaching the eye are not destroyed but remain viable in the ocular tissues, and, by their presence, proliferation and inherent toxicity, produce local lesions in the eye. The character of the resulting lesion is profoundly modified and influenced by the factors of local hypersensitivity and general immunity. The proliferation of the organisms in the eye produces a local hypersensitivity to the bacterial products. This hypersensitivity is of the bacterial type, and a reaction between the hypersensitive tissue and the bacterial products may thereafter result. If the proliferation of the bacteria is not restrained by the forces of immunity, this hypersensitive reaction will be progressive, characterized by inflammation, caseation, necrosis, tissue destruction and often a compensatory overgrowth of granulomatous tissue. If, however, there is present either a natural or an acquired resistance to the infection, the proliferation of the bacteria is restrained, and the reaction is minimal.

W. ZENTMAYER.

## Therapeutics

LOCAL PENICILLIN THERAPY OF HYPOPYON FORMATION, WITH SPECIAL REFERENCE TO USE OF SUBCONJUNCTIVAL INJECTION. A. SORSBY and H. REED, *Brit. J. Ophth.* 31: 528 (Sept.) 1947.

Results of treatment, chiefly with penicillin, are recorded for 66 patients with hypopyon.

This series included 39 patients with infected corneal ulcer; 18 of these were treated with subconjunctival injections of penicillin in doses of 50,000 units, with or without the application of penicillin ointment

in concentrations of 25,000 to 100,000 units per gram of base. Other methods of local penicillin therapy were employed with 12 patients. Two patients received oral treatment with sulfonamide drugs, and 4 others, local penicillin therapy combined with general sulfonamide therapy. For 3 patients, general sulfonamide therapy was used when subconjunctival injections of penicillin proved inadequate.

Twelve patients with hypopyon formation associated with herpetic or neuropathic corneal lesions were treated with various applications of penicillin locally, with or without general sulfonamide therapy. There were also 5 patients with long-standing glaucoma showing hypopyon as a complication. A final group of 10 patients presented 13 instances of hypopyon iritis.

Infected corneal ulcers responded well to treatment. Hypopyon seen in cases of herpetic or neuropathic keratitis gave no response. Hypopyon iritis appeared to require no treatment other than atropine.

A detailed analysis of the cases of infected corneal ulcer with hypopyon in which various types of penicillin therapy were used shows that subconjunctival injection is the method of choice. This therapy was successful in 18 of 21 cases. The mode of treatment is described. It consists essentially in twelve to sixteen subconjunctival injections each of 50,000 units of penicillin (dissolved in 0.25 cc. of 2 per cent procaine hydrochloride and 0.25 cc. of epinephrine hydrochloride [1:1,000]) at intervals of six hours, followed by the instillation of penicillin ointment in a concentration of 100,000 units per gram every four hours.

The following method of preparation of the penicillin for subconjunctival injection was employed: Into an ampule containing 100,000 units of white crystalline penicillin, 0.5 cc. of 2 per cent procaine hydrochloride and 0.5 cc. of epinephrine hydrochloride (1:1,000) are injected. Five-tenths cubic centimeter is now withdrawn and injected subconjunctivally.

W. ZENTMAYER.

USE OF CHOLINE IN OPHTHALMOLOGY. M. MARIN AMAT, Arch. Soc. de oftal. hispano-am. 6: 33 (Jan.) 1946.

The use of choline derivatives in the treatment of glaucoma is well known. The author stresses the value of this drug in the treatment of the following ocular conditions: (1) serpiginous ulcer of the cornea, (2) leukoma of the cornea, (3) purulent iritis consequent to corneoscleral trephination and trauma, (4) incipient panophthalmitis, (5) suppurating socket after enucleation, (6) phlegmonous inflammation after operations for strabismus, (7) chronic dacryocystitis and (8) cholesterol infiltration of the cornea.

A 1 per cent solution of choline with merbromin is instilled. A number of cases are reported in which the disappearance of leukoma with the use of instillations of choline was dramatic.

Reference is made to the oral use of the drug by other authors in the treatment of retinal tuberculosis.

H. F. CARRASQUILLO.

### Toxic Amblyopia

MODIFICATIONS OF THE CRITICAL FUSION FREQUENCY IN THE COURSE OF TOBACCO AMBLYOPIA. F. ROUSSEL and R. WEEKERS, *Ophthalmologica* 113: 215 (April) 1947.

The authors used a method for determining the critical fusion frequency, which they have previously described, in a patient with tobacco amblyopia. They found a lessening of the critical fusion frequency in the region of the fixation point and the blindspot which parallels the extension and density of the centrocecal scotoma. Changes in the frequency of fusion paralleled the improvement in the condition, and the authors state that this is a sensitive method by which to follow the course of the disease, as the lessening of the frequency of fusion can still be demonstrated when the visual acuity has returned to normal and campimetric studies show no further field defects. It is not certain as yet whether these changes in the frequency of fusion are pathognomonic of tobacco amblyopia.

F. H. ADLER.

PATHOGENESIS OF THE LAESIO GANGLII VESICULI OPTICI. J. DE RUYTER, *Ophthalmologica* 113: 276 (May) 1947.

The author calls attention to the fact that in methyl alcohol intoxication the disease process begins in the ganglion cells of the retina and not in the optic nerve fibers. He uses the awkward term "laesio ganglii vesiculi optici" because the optic nerve is not a true peripheral nerve and the disease process should, therefore, not be called a neuritis. He believes that the observations of Burki and Schmid (*Ophthalmologica* 105: 165 and 121, 1943) throw light on the pathogenesis of methyl alcohol poisoning and tabetic primary atrophy of the optic nerve, which also begins in the ganglion cells of the retina. These authors found that only the layer of multipolar cells in the retina contains ascorbic acid. de Ruyter considers that this finding accounts for the involvement of the ganglion cells, since these cells are in an exceptional position as regards the chain of redox reactions governing cellular respiration. Any poisons which impede these redox reactions, in which the vitamins, such as ascorbic acid, are involved, would affect these cells first.

F. H. ADLER.

## Obituaries

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H. MAXWELL LANGDON, M.D.

1876-1947

H. Maxwell Langdon was born in Philadelphia, June 21, 1876, the son of Giles Maxwell Langdon and Frances Jane Smith Langdon. He received his preparatory education at the Rugby Preparatory School; for a time he attended the Collegiate Department of the University of Pennsylvania and received his medical degree at the University of Pennsylvania in 1901. His basic education in ophthalmology was



H. MAXWELL LANGDON, M.D.

1876-1947

acquired at the Royal Ophthalmic Hospital (Moorfields), London, England. At various times, he served as ophthalmologist to the Howard, Children's, Orthopedic, University of Pennsylvania and Presbyterian Hospitals. He was a fellow of the American Medical Association, a member of his county and state medical societies and a fellow of the College of Physicians of Philadelphia, and at one time chairman of the Section on Ophthalmology of the College. He was professor of



ophthalmology in the Graduate School of Medicine of the university, teaching the subject of refraction. He was elected a fellow of the American Ophthalmological Society in 1912. His college fraternity was the Phi Kappa Psi and his medical fraternity the Alpha Mu Pi Omega. He was active in the St. Andrews and in the Pennsylvania Historical Society. He worshiped in the Presbyterian Church.

Dr. Langdon did not contribute largely to the literature, but several of his contributions were notable. He early became interested in the study of the light sense and, together with Mr. H. E. Ives, devised a practical photometer. In 1938 Dr. Langdon reported on the successful use of the thermophore in selected cases of detachment of the retina. His lectures on refraction were delivered tersely and fluently, and were often punctuated by wit and apt anecdotes. In discussions he was outspoken, at times critical and usually enlivening and enlightening. He was widely read, being particularly interested in English and early American colonial history, the events of which he could readily recall with remarkable detail. One of his hobbies was the collection of early prints.

On Nov. 29, 1905 he married Ethel Hancock. He is survived by his wife and daughter, Charlotte.

For many years, Dr. Langdon's activities were restricted by distressing angina, and his death came suddenly from coronary thrombosis, while he was returning to his home in Haverford, Pa., from a vacation in Portsmouth, N. H.

WILLIAM ZENTMAYER, M.D.

## Book Reviews

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**Intracranial Tumors.** Second edition. By Percival Bailey, M.D. Price, \$10.50. Pp. 478, with 16 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1948.

A second edition has permitted Dr. Bailey to correct and bring up to date his well known book on intracranial tumors. A brief atlas of roentgen photographs has been added. Ventriculography and Moniz' method of arteriography are carefully described, as, according to the author, they have greatly increased knowledge of the pathologic nature of a cerebral growth. There is also an excellent study of the hypothalamus, a region of the brain which is gaining in ophthalmologic interest. The importance in diagnosis of the presence of a nonfebrile, steadily increasing alteration in nervous function is emphasized, and this particularly appeals to the ophthalmic specialist, as lesions of the optic pathways are easily open to examination. There is an excellent description of hypophysial tumors, meningiomas and aneurysms, which are all lesions of the most frequent importance to the practicing ophthalmologist.

The text is delightfully clear, and there are no illustrations on annoyingly glossy paper. The ophthalmologist will find this an admirable book of reference.

ARNOLD KNAPP.

**A Short History of Ophthalmology.** Second Edition. By Arnold Sorsby, M.D., F.R.C.S. Price, 8s.6d. Pp. 103, with 7 illustrations. London: Staples Press, 1948.

When the author brought out the first edition of this work in 1933, he wrote as follows: "No attempt has been made to trace the growth of ophthalmology as an organic whole, phase by phase. It was thought more expedient to trace separately the course of the main streams of development." This plan has been left undisturbed in the second edition and has been admirably carried out. In his introduction, he has traced the development of general ophthalmologic knowledge from the time of Hammurabi through the Greek, Arabian, Medieval and Modern Ages. He then discusses the development of the anatomic, physiologic and pathologic knowledge from earliest historical times to the present. Subsequent chapters deal with cataract, glaucoma, therapeutics, spectacles and the ophthalmoscope. The book closes with a chapter on ophthalmology in the British Isles.

It is difficult to review this somewhat condensed type of work, but certain statements can be repeated to illustrate the interest and fascination aroused by reading it. It is entertaining to read that the Babylonians practiced couching for cataract; that the Egyptians knew of most diseases of the lids, from chalazion to dacryocystitis; that Roger Bacon wrote of convex lenses for presbyopia, and that da Vinci "either realized or came near to realizing" the principle of the camera obscura as applied to the eye. Here one finds the earliest anatomic drawing of the eye (Hünain ibn Is-hâq) and learns with surprise

the soundness of some of Hippocrates' and Galen's observations. The essential feature of glaucoma—hypertension—is generally thought to have been recognized in 1840, but Sorsby quotes Banister (1622) as "rubbing upon the eie-lids" to find if the "eye be growne more solid and hard than naturally it should be." The magnet was used to remove foreign bodies from the eye as early as 1627, and the first tattooing of the cornea was performed by Galen. Of interest (in view of contrary opinions so long and widely held) is Sorsby's contention that the Chinese learned about spectacles from the Europeans by way of Malacca. Glasses were certainly mentioned—and the sources are quoted—in 1299 and 1305. In fact, painters working in the fourteenth century endowed even biblical figures with these accessories.

These excerpts may serve to indicate to the potential reader that he should obtain this little book. I am sure that he will enjoy it.

G. M. BRUCE, M.D.

**Bulletin of the Ophthalmological Society of Egypt.** Volume XXXV.  
Pp. 196. Cairo, Egypt: Imprimerie Misr, 1948.

This bulletin brings a report of the proceedings of the Ophthalmological Society of Egypt during its thirty-ninth session, in 1942. Dr. Mohammed Mustafa El Bakry was president, and Dr. Mohammed Khalil, secretary. In addition to the president's address, the principal subject of discussion is syphilis of the eye. The other contributions cover a wide range of clinical features and include an illustrated article by Dr. Rowland P. Wilson, entitled "The Histopathology and Significance of Bulbar Follicles." The author concludes that the bulbar follicles are not trachoma follicles in the ordinary sense of the word but are lymph nodules formed *de novo* in the conjunctiva.

ARNOLD KNAPP.

## SUCCESSFUL DIATHERMY TREATMENT OF RECURRING RETINAL HEMORRHAGE AND RETINITIS PROLIFERANS

Report of a Case

F. H. VERHOEFF, M.D.  
BOSTON

**R**ECURRING RETINAL hemorrhage in young persons is frequently associated with ophthalmoscopically recognizable periphlebitis. In most cases the patient gives a cutaneous reaction to tuberculin, and in the cases in which the retina has been examined microscopically nodular foci of epithelial cells have been observed along the veins. These facts constitute strong evidence that the condition termed by Igersheimer "periphlebitis adolescentium" is an entity, that it is caused by tuberculosis and that to it most cases of so-called Eales's disease belong. It is uncertain whether the periphlebitis is directly hematogenous or results from dissemination of the infection by way of the vitreous. Microscopically, I have seen such foci along retinal veins in the vicinity of localized active foci of tuberculous chorioretinitis, and there they were obviously due to migration of infected macrophages within the vitreous. The hemorrhages evidently result from engorgement of capillaries and small veins. When this engorgement is severe and persistent, new vessels are formed, which may extend into the vitreous. At the same time, hemorrhage into the vitreous usually occurs, and the extravasated blood becomes organized by the new vessels, thus producing typical retinitis proliferans. Periphlebitis is not certainly the immediate cause of the capillary engorgement and hemorrhages, for in some cases, including those of retinitis proliferans, it is not visible, and even in cases in which it is conspicuous it is often not so situated as to explain the hemorrhages. It would seem, therefore, that the vascular lesions causing the hemorrhages are usually too small to be visible with the ophthalmoscope.

For this condition, treatment heretofore used, including injections of tuberculin, has been of doubtful value. So far as I know, the present case is the only instance of recurring hemorrhages in which diathermy treatment has been employed.

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Read at the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Spring, Va., June 6, 1947.

## REPORT OF CASE

*History.*—H. T. H. was first seen by me on Aug. 10, 1939, when he was 18 years of age. With a correction of  $-0.37$  cyl., axis 180 for the right eye and of  $-0.37$  cyl., axis 165 for the left eye, vision was 20/15— in each eye. There was 3Δ of exophoria. The fundi, pupils and visual fields were normal. Glasses were not ordered.

On May 25, 1943 the patient entered naval service as ensign, and about April 15, 1944, while on submarine duty, he noticed blurred vision in the right eye. This cleared up but recurred five weeks later, so that ever afterward he had to use the left eye for periscopic observations. He was sent to a naval hospital on July 11,<sup>1</sup> where, on September 8, vision in the right eye was observed to have cleared to 20/40. Shortly after this, while he was at home on leave, vision in the right eye was reduced to light perception, but on October 28 it had cleared to 6/20. On December 4 vision again failed in the right eye and has never since been better than ability to count fingers at 2 feet (60 cm.).

The Naval medical service in 1944 made a diagnosis of hemorrhage into the vitreous and retinitis proliferans in the right eye. General physical examination, including a roentgenographic study of the chest and paranasal sinuses, revealed nothing remarkable. Agglutination tests gave negative reactions for typhoid the paratyphoid bacilli, *Proteus vulgaris* OX19 and *Brucella abortus*. The cutaneous reaction to tuberculin was positive. A later test, made on Feb. 15, 1945, with a dilution of 1:100,000, gave a 3 plus reaction.

For two months the patient was given, without benefit, biweekly or weekly injections of old tuberculin U.S.P. He was also given potassium iodide; later, large doses of ascorbic acid, and, finally, injections of penicillin. These substances were believed to have been of some benefit but did not completely check the process, and on Jan. 3, 1945 hemorrhages were noted in the left eye. With regard to this finding, Comdr. Raymond E. Meek wrote me from the United States Naval Hospital, Newport, R. I.: "At present the left eye has vision of 20/20, but above and temporal to the macula are small droplets of blood hanging down into the vitreous, and strands of what appears to be exudate coming away from the retina, with new vessels growing into it." The patient was discharged from the Navy on May 1, 1945.

*Ophthalmic Examinations.*—The patient had consulted me on Sept. 6, 1944, while still in naval service. The right eye showed two foci of retinitis proliferans, one a short distance nasal to, and the other below, the optic disk. Between the disk and the macula were a number of small exudates, such as occur in circinate retinitis (lipid deposits). The inferior temporal vein was sheathed in white for a considerable distance. There were a number of hemorrhages in the retina and a gray mass of old blood in the vitreous below. Vision in the right eye was 20/40. The left eye was normal; its visual acuity was 20/15—.

Feb. 13, 1945: The patient again consulted me. The vitreous of the right eye was full of blood. The left eye showed retinal hemorrhages in the upper outer quadrant, but its visual acuity was still 20/15—.

February 24: The patient came to Boston on terminal leave and placed himself under my care. Treatment with "diasone" (the disodium formaldehyde

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1. While the patient was in the hospital, an ammunition depot 2 miles (32 kilometers) away blew up. The patient left the hospital without permission and assisted in extinguishing the fire in several cars loaded with ammunition. For this he was awarded the Navy Marine Corps Medal.

sulfoxylate derivative of diaminodiphenylsulfone) was begun, and the patient was instructed to see me weekly.

March 10: Morning temperatures taken recently had ranged from 96.7 to 97 F.

April 14: There were definite retinitis proliferans in the upper outer quadrant of the left eye and fairly large retinal hemorrhages still farther out.

April 28: The vessels extended farther into the vitreous of the left eye. In the crotch between the two branches of a retinal vein near the area of retinitis proliferans was a round white spot (periphelebitis) about  $\frac{1}{3}$  disk diameter in size, and next to this, a smaller white spot. The new tissue in the vitreous had increased. Vision in the left eye was 20/15—. The treatment with "diasone" was discontinued, and diathermy was decided on.

May 8: A canthotomy was performed on the left eye. The sclera was exposed in the upper outer quadrant. Several weak and three strong applications of surface diathermy were made over the affected region of the retina. Ophthalmoscopic examination then showed extensive white areas in this region. There was no hemorrhage into the vitreous.

May 15: Small hemorrhages were seen in the white areas.

May 22: The white areas were turning gray and showed pigmentation around them. Vision in the left eye was 20/15—. Potassium arsenite solution U.S.P. was prescribed.

October 8: The treated areas were atrophic and pigmented. Delicate tissue (old retinitis proliferans) still extended into the vitreous but was free of visible vessels. There were no retinal hemorrhages.

Feb. 13, 1946: This morning the patient had noticed some disturbance in the upper outer quadrant of the visual field of the left eye. Several fresh retinal hemorrhages were seen at, and anterior to, the equator of the eye, in the lower inner quadrant. Vision was 20/15—. Diathermy was decided on.

February 15: The retinal hemorrhages had increased in number and now involved the region from 2 to 5 o'clock. At operation, the sclera was exposed below and the tendon of the inferior rectus cut. Numerous nonperforating diathermy points (0.5 mm.) were applied in the region of the hemorrhages. Ophthalmoscopic examination then showed the treated areas to be almost continuous.

February 16: There were many new hemorrhages above the treated region. Some were near the fovea.

February 27: The patient was discharged from the hospital.

March 2: The retinal hemorrhages had mostly disappeared. A small streak of blood, which may previously have been overlooked, extended into the vitreous from below. The vitreous was filled with fine, dustlike opacities. Vision in the left eye was 20/20— with a correction of  $-0.50$  sph.  $-0.75$  cyl., axis 190.

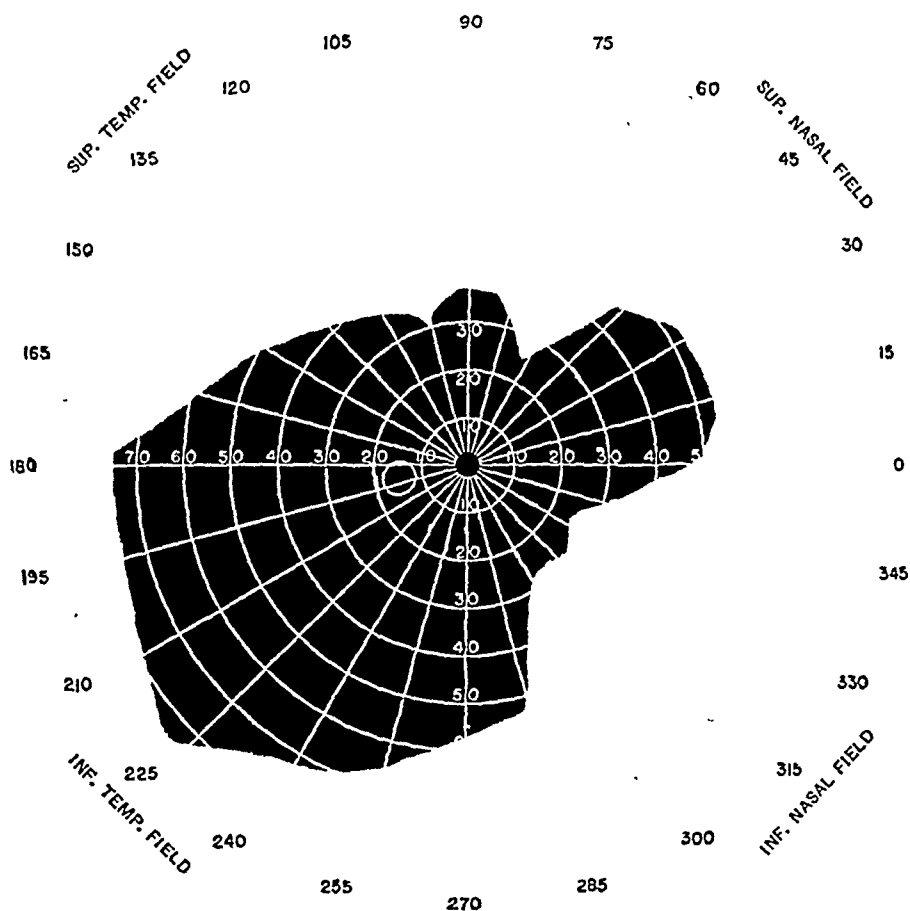
May 6: The right eye diverged. The fundus was not visible. Vision was limited to perception of hand movements in this eye. Numerous nonperforating diathermy points were applied in the lower half of the eye.

May 13: The upper half of the right eye was treated in the same way as the lower half.

May 5, 1947: Right eye: The fundus was still invisible. Tension was normal. Vision was limited to counting fingers at 1 foot (30 cm.). Left eye: There have been no new hemorrhages. The treated areas were atrophic and pigmented. The visual field (figure) indicates their location. Vision was 20/30— without correction and 20/15— with a correction of  $-0.25$  sph.  $-0.75$  cyl., axis 165.

## COMMENT

When this patient came under my care, vision seemed to be hopelessly lost in the right eye, and retinitis proliferans indicated the same fate for the left eye. "Diasone" had been sent me for trial in cases of ocular tuberculosis, and I therefore tried it with this patient. No improvement having occurred in two months, this treatment was abandoned. It then occurred to me that diathermy treatment, such as is used for detachment of the retina, might check the process in the left eye and, at the same time, fasten down the retina so that it could not be pulled off as a result of



Contraction of the visual field of the left eye produced by diathermy.

the retinitis proliferans. Presumably, this treatment would destroy the inflammatory foci, whether tuberculous or not, and thus prevent dissemination of infection from them. It would also obliterate the vessels from which the hemorrhages arose. Accordingly, surface diathermy was applied to the affected region in the left eye. When the reaction had subsided, the treated areas presented an appearance similar to that after successful diathermy treatment of detached retina. The foci of periphlebitis had been destroyed, and the hemorrhages had disappeared. Deli-

cate tissue resulting from the previous retinitis proliferans still projected into the vitreous, but it was free from visible vessels. Beneath it, the retina was fused with the choroid and hence was no longer in danger of being pulled off. Visual acuity with glass was 20/15—.

The condition of the left eye remained unchanged until nine months later, when the patient noticed slight visual disturbance, although his visual acuity was still 20/15—. I found a number of large retinal hemorrhages at the periphery of the retina in the lower inner quadrant. In the course of two days the region from about 8 to 5 o'clock was covered with hemorrhages. No periphlebitis was recognizable. Since these hemorrhages were remote from the previously treated retinal area, it is probable that they were due to fresh hematogenous infection. The entire hemorrhagic region was then subjected to diathermy, as described. Numerous additional hemorrhages produced by this treatment seemed alarming at the time, but all the blood had disappeared at the end of about three weeks. Up to time of this report, fifteen months after the second episode, there has been no recurrence of hemorrhage in the left eye.

As a result of the treatments, the visual field is, of course, considerably constricted, but the patient is not aware of any handicap from this source. There has also been produced a slight amount of myopia and an increase in myopic astigmatism. Whereas before the treatments the visual acuity of the left eye was 20/15—, a glass is now required to obtain this vision, and without glass the visual acuity is only 20/30—.

Although vision in the right eye seemed to be hopelessly lost, numerous applications of diathermy were made around the entire equator of this eye, after it had become apparent that the treatment of the left eye was successful. Persisting cloudiness of the vitreous still makes it impossible to determine whether this treatment has been of benefit. Probably useful vision could have been saved in this eye if the diathermy had been used while the vitreous was still clear and central vision was fairly good.

It is probable that the patient has now passed through the period of liability to recurrence of hemorrhages. If, however, retinal hemorrhages again occur in the left eye, I shall treat the affected areas with diathermy to the extent to which I can do so without endangering central vision.

There is still another way in which diathermy may possibly be of benefit, not only in selected cases of tuberculous periphlebitis but in cases of retinal vascular obstruction from any cause. It may establish communication between retinal and choroidal vessels and thus restore retinal circulation. The appearances I noted in some of the treated areas in the present case strongly indicated that such a communication had been made. It would seem, therefore, that attempts to establish by this or other means such collateral circulation should be made in all cases of impending blindness from obstruction of retinal vessels. These cases would in-



clude those of partial obstruction of the central vein or artery, cases of pronounced sclerosis of the retinal vessels with impending impairment of central vision and early cases of circinate retinitis. In cases of complete obstruction of the central vein the treatment might at least prevent the development of hemorrhagic glaucoma. It might even offer some hope in cases of diabetic retinopathy.

The possible establishment of a collateral circulation also offers hope in cases of retinitis proliferans arising from the disk or its vicinity. Here, of course, the affected vessels cannot safely be obliterated by diathermy, but establishment of a collateral circulation near the disk might relieve the venous congestion and thus check the proliferation of new vessels.

395 Commonwealth Avenue.

### DISCUSSION

DR. ARTHUR J. BEDELL, Albany, N. Y.: I shall show several photographs in the latest case of angiomatosis in which I have operated. The first, taken three months before the last, shows immense dilatation of the superior temporal artery and vein, exudate in and about the macular region and, far to the temporal side, the well demarcated angioma, with fine capillaries on its surface. After multiple diathermy punctures, the exudate was less and the angioma flatter, with dark but not black scars, representing much less destruction than that after a strong diathermy current.

With regard to diathermy, I suggest a word of warning, for two reasons: First, it is impossible accurately to control the delivered current in a great group of vessels, and, second, many changes ascribed to the treatment may be those which would have occurred had nature not been interfered with. The procedure should be tried on animals before it is recommended for use on human subjects.

DR. RALPH C. RYCHENER, Memphis, Tenn.: I was interested in Dr. Verhoeff's suggestion that his procedure be used for certain vascular obstructions, particularly obstruction of the central vein. Does Dr. Verhoeff think that in a case of complete obstruction of the central vein such an attempt would be worth while?

DR. F. H. VERHOEFF, Boston: The suggestion of using diathermy in cases of obstruction of the central vein is based on theoretic considerations. The possibility of establishing communications between the choroid and the retinal circulation is something that should be worked on experimentally. The outlook in these cases is so hopeless that it is justifiable to carry out the experiments on human subjects. If visual acuity is already practically abolished, no return is to be expected; but if one could get the retinal circulation established secondary glaucoma might be prevented. Experimental investigation should be carried out to determine whether much, or only a little, heat should be applied. I should do the experiments on dogs, not rabbits. With such a wonderful circulation as exists in the choroid, it seems too bad not to utilize it when the circulation in the retina is lost.

# OCULAR CHANGES ASSOCIATED WITH SCRUB TYPHUS

A Study of Four Hundred and Fifty-One Patients

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PHILADELPHIA

VARIOUS OCULAR changes associated with scrub typhus (mite-borne typhus tsutsugamushi fever) were described by me in reports submitted to the Office of the Surgeon General of the United States army in 1944 and 1945. Abstracts of these reports were released in the *Bulletin of the United States Army Medical Department* in April 1945<sup>1</sup> and April 1946.<sup>2</sup> The external ocular changes consisted of conjunctival injection, occurring during the onset of the disease, and occasionally, subconjunctival hemorrhages, appearing during the first ten days. The intraocular changes, previously undescribed, were more noteworthy. The commonest, and most striking, of these was edema of the disk and retina, occurring during the second and third weeks of the disease and persisting well into convalescence. Retinal hemorrhages, usually superficial in type, and white, soft exudates occurred in a smaller number of patients. When these did occur, they were usually associated with edema of the disk and retina.

Subsequent to my original report, Macaskill,<sup>3</sup> in October 1945; Dame,<sup>4</sup> in November 1945, and Donegan,<sup>5</sup> in January 1946, reported ocular changes occurring with scrub typhus. Macaskill studied 70 pa-

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Submitted as a candidate's thesis in partial fulfilment of the requirements for membership in the American Ophthalmological Society, 1947.

\*Formerly Major, Medical Corps, Army of the United States.

1. Scheie, H. G.: Ocular Changes in Scrub Typhus, Bull. U. S. Army M. Dept., April 1945, no. 87 p. 37.

2. Scheie, H. G.: Ocular Changes in Scrub Typhus, Bull. U. S. Army M. Dept. 5:423 (April) 1946.

3. Macaskill, J.: Some Ocular Complications of Scrub Typhus, Brit. J. Ophth. 29:537, 1945.

4. Dame, L. R.: Eye and Ear Sequelae of Scrub Typhus Fever, Bull. U. S. Army M. Dept. 4:554 (Nov.) 1945.

5. Donegan, E. A.: Ocular Findings in Tropical Typhus, Brit. J. Ophth. 30:11 (Jan.) 1946.

tients. He found subconjunctival hemorrhages in 4 patients, intense engorgement of the retinal veins in 7 patients, papilledema in 4 patients, retinal hemorrhages in 1 patient and bilateral atrophy of the optic nerve in 1 patient, seen six months after the acute stage of the illness. No pathologic studies were made. Dame examined 50 patients during convalescence. He found nonspecific hyperemia of the optic disks. No other retinal changes were noted. He observed greatly enlarged blindspots in most of the eyes and contraction of the visual fields in some, the amount averaging 15 degrees. Ten eyes showed scotomas. No permanent loss of

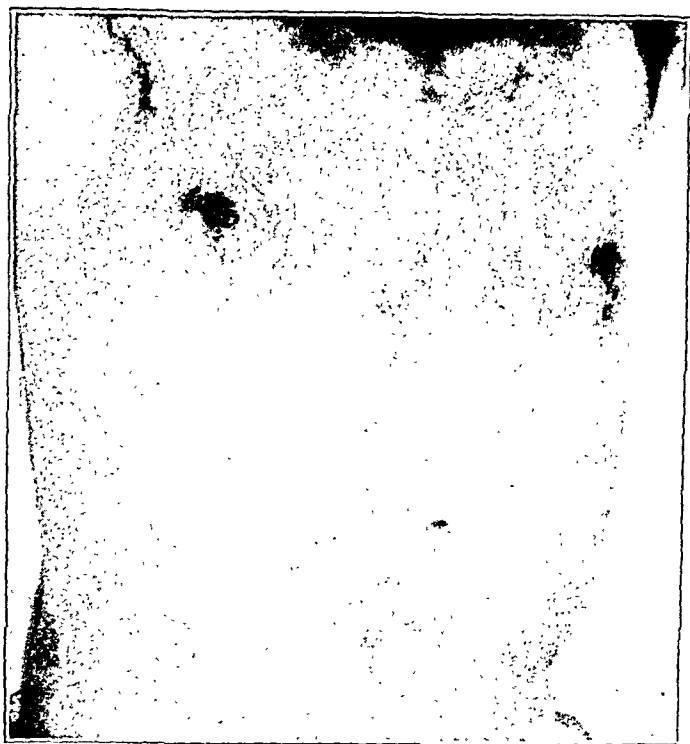


Fig. 1.—Typical primary lesion, containing an eschar. Army Institute of Pathology, Washington, D. C.

visual acuity was noted. Donegan observed 101 patients. He reported on 32 patients showing haze of the vitreous. Seventeen of his patients had papilledema, which he interpreted as due to vascular disturbance, and not true neuritis. Other patients showed blurring of the disks, not interpreted as papilledema.

The present study describes, in some detail, the ocular changes observed in the routine examination of 451 patients with scrub typhus. Pathologic studies were carried out on eyes removed at autopsy from 9 of these patients. An attempt will be made to correlate the ophthalmologic and the general clinical findings.

## CLINICAL PICTURE

Scrub typhus is an acute febrile illness caused, as demonstrated by Lewthwaite and his associates,<sup>6</sup> by *Rickettsia ripponica*. The rickettsia is transmitted by the larval form of a mite, *Trombicula akamushi*, family Trombidiidae, order Acarina. The disease is endemic in China, India, Burma, the Federated Malay States, Indo-China, Japan, Netherland East Indies, New Guinea, the Solomon Islands and North Queensland. A

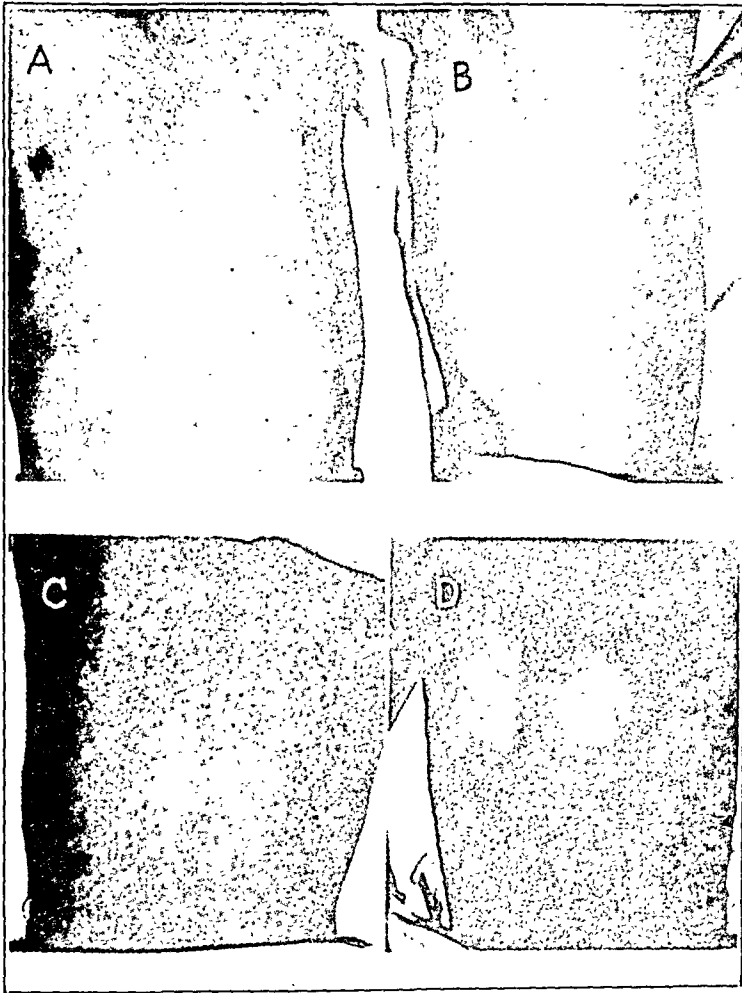


Fig. 2.—Appearance of the rash of scrub typhus. *A*, sparse maculopapular rash on the fifth febrile day; *B*, fine, discrete rash, largely macular, on the sixth day of fever; *C*, well developed maculopapular rash on the eighth febrile day; *D*, blotchy, coarse maculopapular rash on the tenth day of fever (after Sayen and others<sup>8</sup>).

papule develops at the site of the mite bite and usually progresses to formation of an ulcer, 5 to 7 mm. in diameter, characteristically containing a black eschar (fig. 1). The eschar was seen in 60 per cent of the the series. It can occur anywhere on the body. The incubation period is estimated to be from ten to nineteen days, followed by relatively abrupt onset of the disease. The onset is characterized by chilliness, fever, malaise, headache and generalized aching. The elevation of temperature increases

during the first week of the disease, until in most instances it reaches 103 to 105 F. Wide daily fluctuations in the temperature are characteristic. The fever usually subsides by lysis during the third week of the disease.

A rash, which is macular or maculopapular in type and involves the trunk, and sometimes the face and extremities, appears in most patients from the third to the sixth day of the disease (fig. 2). It lasts from three to five days. Ninety to 95 per cent of the patients in the present series showed generalized lymphadenopathy. Regional adenopathy is usually present with appearance of the eschar. Splenomegaly occurred in 34 per cent. The patient is apathetic. Conjunctival injection is common. Early in the disease many patients have a cough and the physical signs of bronchitis. As the severity of the illness increases, typhus pneumonia may occur, with tachypnea, hyperpnea and cyanosis. The blood pressure is usually low during the febrile stage. Myocarditis may develop, but congestive heart failure is rare. The central nervous system is frequently affected. The manifestations are muscular twitching, paresthesia, transient diminution of hearing, confusion, delirium and convulsions. Nystagmus occurs much more rarely. Renal damage is not infrequent in severe cases. The fever usually terminates in two to three weeks, after which prolonged convalescence occurs.

Diagnosis of the disease is usually not difficult in endemic areas, especially when the eschar, lymphadenopathy and rash are present. The Weil-Felix test is an important confirmatory means. A significant agglutination titer against *Proteus vulgaris* O X K is found in a majority of patients, while an insignificant titer is obtained against the O X 2 and O X 19 strains. The positive reaction is usually obtained during the third week of the disease. The mortality in the armed forces has ranged from 2 to 10 per cent. The prognosis is best in young persons who have previously been in good general health and who can be given early hospital care. No specific treatment is available, the therapeutic steps being rest, good nursing and supportive measures. No protective vaccine for man has as yet been developed. Clothing impregnated with dimethylphthalate and dibutylphthalate is protective. The mites are most prevalent in areas of scrub jungle overgrowth, particularly along rivers subject to floods. Lying or sleeping on the ground in such places should be avoided.

#### SOURCE OF MATERIAL

The ophthalmologic studies reported here, all made by me in the capacity of chief of the ophthalmologic section, were part of a general clinical study of the disease carried out by the medical service of the Twentieth General Hospital from October 1943 to February 1945. A total of 616 cases were made available. All

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6. Lewthwaite, R., and Savor, S. R.: Typhus Group of Diseases in Malay, *Brit. J. Exper. Path.* 17:1 (Feb.); 461 (Dec.) 1936.

the patients had contracted the disease in Assam and Burma, where scrub typhus, hitherto unsuspected, became manifest during the North Burma campaign of 1943 to 1945. The results of this work have been reported by Machella and Forrester<sup>7</sup> and Sayen, Pond, Forrester and Wood.<sup>8</sup> Most of the statistics cited here were obtained from a series of 200 consecutive patients studied in detail by Sayen and associates.<sup>8</sup> Adequate ophthalmologic data were recorded on 451 of the 616 patients. The data correlating the ocular and the general clinical findings were derived from studies on 159 of the 200 patients just mentioned.

### METHOD OF OPHTHALMOLOGIC STUDY

The first patients who were admitted to the Twentieth General Hospital with scrub typhus presented a perplexing diagnostic problem. The personnel were unfamiliar with this disease and were further misled by the fact that scrub typhus had not previously been reported from the area of India and Burma in which we were stationed. In consequence, numerous diagnostic tests and consultations were carried out, including an ophthalmologic study. The eyegrounds of these first patients were examined at least twice weekly, in the hope of finding some bit of evidence that might be of diagnostic value. This undoubtedly led to the discovery of the lesions in the fundus, since they develop late in the disease, with onset during the second and third weeks.

Unusual ocular changes were seen to develop in a rather large number of patients. Therefore, when the disease was recognized and greater numbers of these patients were admitted to the hospital, ocular examinations were carried out routinely. Every patient admitted to the hospital who was suspected of having scrub typhus was subjected to ophthalmic examinations once a week or oftener, with the pupils dilated. Visual acuity was determined for all patients with Snellen type at a distance of 20 feet (6 meters) or with Jaeger type at reading distance, and the visual fields were taken for most of the patients with retinopathy as early as this could be done. Peripheral fields were determined on a perimeter having a radius of 330 mm. with a 1 mm. white test object, and central fields were plotted with the same test object on a tangent screen at 1 meter. Examinations with the slit lamp could be performed only during convalescence, when the patient was brought to the clinic. The observations are recorded under two headings: extraocular and intraocular.

### ROUTINE OPHTHALMOLOGIC OBSERVATIONS

#### EXTRAOCULAR EXAMINATION (FIG. 3)

*Conjunctival Injection.*—Conjunctival hyperemia was prevalent during the early stages of the disease, usually with no discharge, and tended to disappear during the second and third weeks. During the second week, when we first saw some of the patients, the hyperemia may have subsided. Nevertheless, hyperemia was present in 174 patients (38.8 per cent of the entire series). Cultures of secretions from the conjunctiva

7. Machella, T. E., and Forrester, J. S.: Mite Typhus: Clinical and Laboratory Study of Sixty-Four Cases, *Am. J. M. Sc.* **210**:38 (July) 1945.

8. Sayer, J. J.; Pond, H. S.; Forrester, J. S., and Wood, F. C.: Scrub Typhus in Assam and Burma: Clinical Study of Six Hundred and Sixteen Cases, *Medicine* **25**:155 (May) 1946.

showed no significant incidence of pathogenic organisms, and conjunctival scrapings were negative for inclusion bodies.

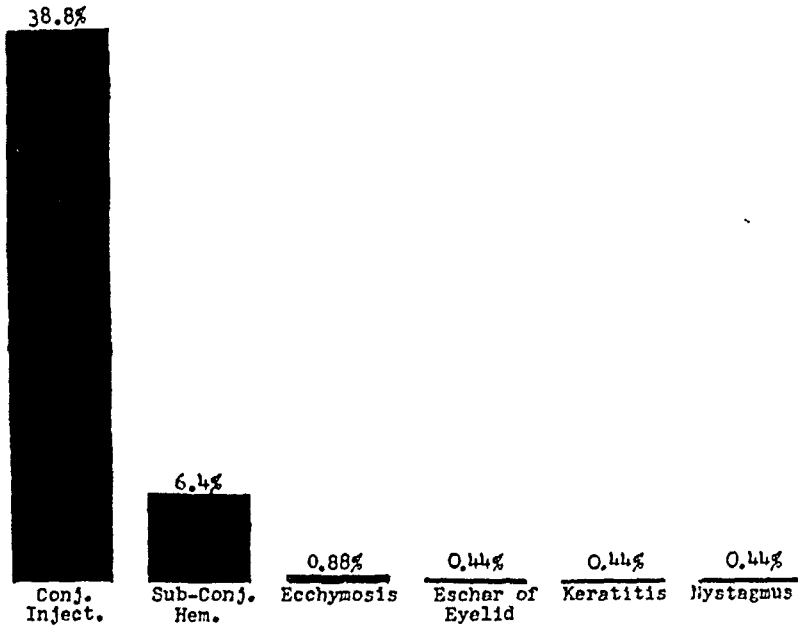


Fig. 3.—Incidence of extraocular changes. Army Institute of Pathology, Washington, D. C.



Fig. 4.—Bilateral subconjunctival hemorrhages. Army Institute of Pathology, Washington, D. C.

*Subconjunctival Hemorrhages.*—Bulbar subconjunctival hemorrhages, presenting a striking appearance, occurred in 29 patients (6.4 per cent) during the first ten days of the disease. In 18 they were bilateral and in

11 unilateral (fig. 4). As a rule, the hemorrhages were massive, at times covering one third to one half of the exposed sclera.

*Ecchymosis of the Eyelids.*—Ecchymosis of the eyelids was seen in 4 cases. This also occurred early in the disease.

*Eschar of the Eyelids.*—An eschar, typical of the primary lesion of the disease, the result of a mite bite, was seen involving the upper lid of 2 patients (fig. 5).

*Keratitis.*—Ulcerative keratitis occurred in only 2 patients. In both instances it was believed to be nonspecific and of the type due to corneal exposure in very sick patients.

*Nystagmus.*—In 2 patients an unusual type of nystagmus developed during the course of their disease. The nystagmus was manifested by coarse, irregular, jerky, incoordinate movements of the eyes from side to side while the patient attempted to fix on an object. The amplitude of

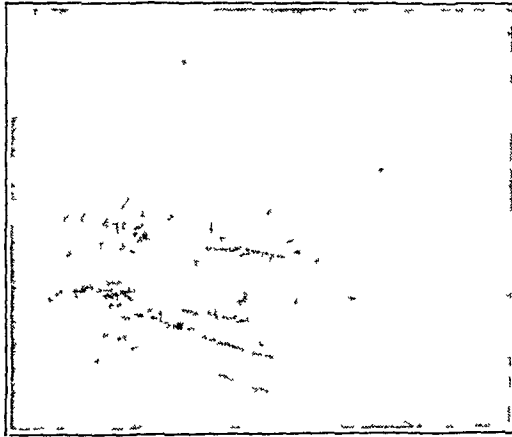


Fig. 5.—Primary lesion of the eyelid. Army Institute of Pathology, Washington, D. C.

the movements gradually diminished as fixation was accomplished. The eyes would then remain quiet until fixation on another object was attempted. The movement greatly resembled the type of incoordination seen in extremities associated with cerebellar lesions and could well be called "fixation" nystagmus.

#### OPHTHALMOSCOPIC EXAMINATION (FIG. 6)

*Vascular Changes.*—Engorgement of Veins: As in the original study, venous engorgement was the most consistent finding and always preceded the other intraocular changes. It occurred in 67.2 per cent of the entire series of 451 patients. The onset was noted during the first or second week of the disease. When the disease was progressive, venous engorgement increased, until not infrequently the veins were two to two and one-half times the diameter of the arteries. As venous engorgement progressed, the following vascular changes developed:



(a) Irregularity in Caliber of Veins: The veins were noted to become irregular in caliber as the engorgement increased. This change was particularly noticeable in the region of the disk, especially along the inferior temporal veins. The veins frequently appeared sausage like, due to localized dilatation, this appearance being accentuated by increased tortuosity of the vessels.

(b) Blurring of Outlines of Veins: Accompanying the dilatation and irregularity of the veins was haziness of the outline of their walls, especially in the region of the disk. This was not due to a definite perivascu-

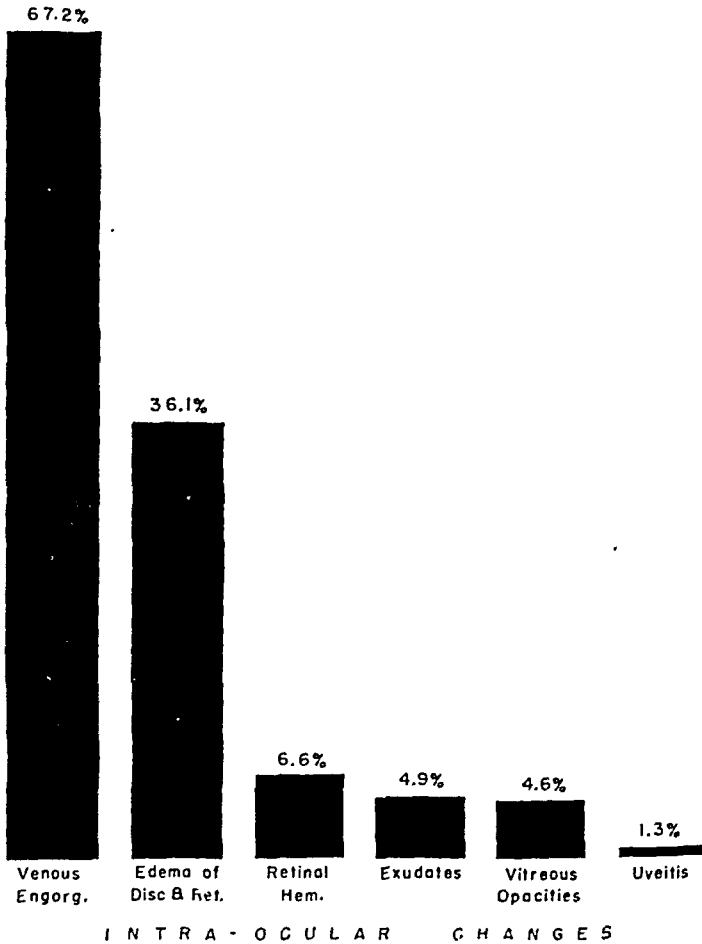


Fig. 6.—Incidence of intraocular changes. Army Institute of Pathology, Washington, D. C.

lar sheath, but appeared instead to be a veil-like phenomenon. Part of this appearance could no doubt be explained by retinal edema, with a somewhat blurred appearance of the entire posterior pole of the eye. Even though the arteries near the disk were often hazy, they never showed a degree of veiling comparable to that of the veins. For this reason, it was felt that fibrinous exudate was escaping from the vessels. Further support of this was given by the presence of occasional hemor-

rhages, which appeared to be in the outer coats of the veins, or adjacent to them along their walls.

(c) *Thrombosis of Veins*: Though thrombosis of the retinal veins appeared imminent in many cases, as judged by their extreme engorgement and their irregularity, it was observed only once in the entire series. The patient was unusually ill, and the course of his disease was protracted. The thrombosis was bilateral, involving the inferior temporal vein of his right eye and the inferior nasal vein of his left eye.

(d) *Arteriovenous Crossing Phenomenon*: As the venous engorgement became more pronounced, the veins appeared to be compressed, and frequently interrupted, at the arteriovenous crossings. The reason for this

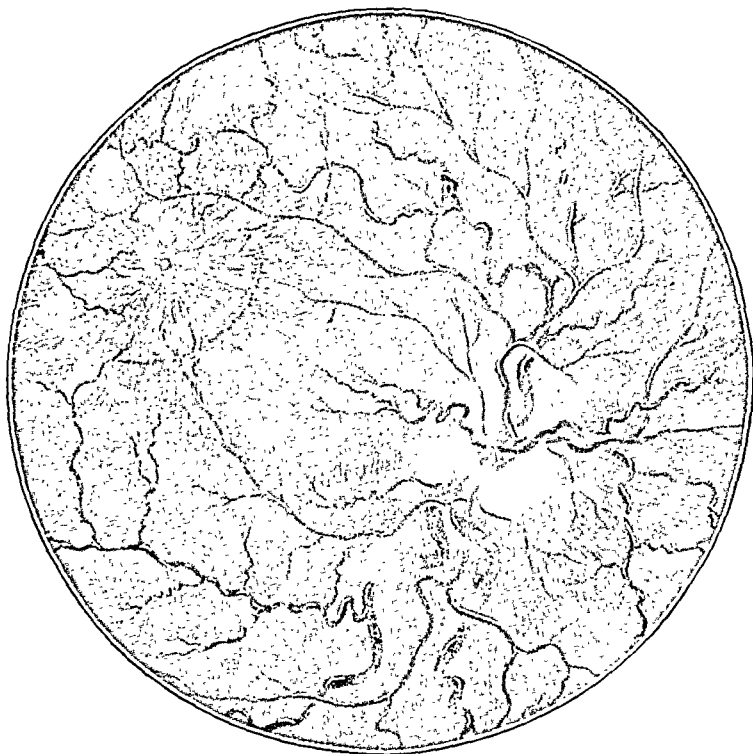


Fig. 7.—Drawing of the fundus, showing edema of the disk, venous engorgement and changes in arteriovenous crossings. Army Institute of Pathology, Washington, D. C.

is not clear. The compression could have been due to localized indentation of the distended venous wall by the more resistant wall of the artery. The interruption seemed to be caused by an exudation at the arteriovenous crossing, filmy in type, obscuring the venous wall adjacent to the artery.

(e) *Arterial Changes*: Changes in the retinal arteries appeared to be secondary to the other changes in the eyegrounds. The most remarkable of these was the exudation at the arteriovenous crossings, but this was a diffuse veil rather than a periarterial or a perivenous sheath. At times the arteries seemed pale, but this was difficult to evaluate. Near the

margins of the disk the arteries were often obscured and seemed to show sheathing, but the entire area around the disk was affected to an equal, or a greater, degree.

*Edema of the Disk and Retina.*—Edema of the disk and retina (fig. 7) was seen in 163 of the 451 patients (36.1 per cent). It was the commonest manifestation of retinopathy. It was always preceded by engorgement of the retinal veins. It was always bilateral and both the disk and the retina were always involved, though to varying degrees. In some cases it resembled papilledema due to increased intracranial pressure, but the swelling was never very great, usually less than 1.5 D. and never over 2.5 D. Moreover, the posterior pole of the eye was diffusely edematous. The retinal edema and that of the disk were usually of about the same magnitude. Less often the retina showed pronounced edema and the disk almost none. The criteria for edema of the disk were definite elevation of the nerve head and blurring and obscuring of margins of the disk, most prominent at the nasal side and at the upper and lower poles. The presence of edema of the retina was established by the irregular light reflexes from the retina, the wavy, tortuous course of the veins and the translucent retinal folds running parallel to the temporal margins of the disk. In many cases these folds radiated from the macula also. The physiologic cups tended to be filled. The disk and the surrounding retina showed increased capillarity and a veiled, somewhat opaque, appearance. Edema of the disk and retina appeared during the second or third week of the disease. It persisted for one or two weeks and then began to subside slowly, often being apparent for several weeks after defervescence.

*Retinal Hemorrhages.*—Retinal hemorrhages were observed in 30 of the 451 patients (6.6 per cent). In 24 patients they were superficial (flame shaped or striate). Three patients had deep punctate hemorrhages in the macular region. Two others had preretinal hemorrhages. In the patient in whom thrombosis of the retinal veins developed, hemorrhages of all types were seen. The hemorrhages were unilateral in 25 patients, usually occurring singly at the posterior pole of the eye, not far from the disk. Except in 3 instances the hemorrhages were associated with edema of the disk and retina. They usually appeared at the time when the edema of the disk and the vascular changes were most marked.

*Retinal Exudates.*—Fluffy, white exudates were observed in 22 patients (4.9 per cent) of this series. They were usually of the cotton-wool variety; a few resembled ganglioform degeneration. They occurred singly in 19 patients and were multiple in 3. With 1 exception, the exudates were associated with edema of the disk and retina. They occurred at about the same time as the retinal hemorrhages and had the same distribution. They were associated with retinal hemorrhages in 9 eyes.

*Uveitis and Opacities of the Vitreous.*—Definite uveitis was seen in 6 patients (1.3 per cent). Opacities of the vitreous without cleancut evidence of uveitis were seen in 21 patients (4.6 per cent). The opacities were dustlike and most numerous in the posterior portion of the vitreous. The uveitis was remarkably asymptomatic except in 1 patient, in whom secondary glaucoma developed. Usually the only complaints were photophobia and slightly blurred vision. Ciliary injection was noted in only 2 of the 6 patients. All the patients with uveitis had keratic precipitates, a pronounced aqueous flare, and many floating clumps of cells, and 1 had Koeppe nodules. Of the 21 patients showing opacities of the vitreous without uveitis, 18 had retinal edema. The other 3 showed intense venous engorgement. Of the 6 patients with uveitis, 4 showed retinal edema.

#### ONSET AND DURATION OF RETINOPATHY

The appearance of retinopathy could usually be anticipated when venous engorgement became intense. However, the diagnosis was not made except on the basis of edema, hemorrhage or exudate. These manifestations occurred as early as the seventh day, but usually appeared from the tenth to the seventeenth day. The duration of the retinopathy varied considerably. The average time of disappearance was the eighth week of the disease. In some eyes it persisted as long as thirteen or fourteen weeks. No residual effect on visual function was detected, although in a small number of patients a mild pigmentary disturbance, possibly due to retinal atrophy, was seen adjacent to the macula.

#### VISUAL FUNCTION

Visual acuity was determined routinely. No definite evidence of visual defect was observed in any patient with retinopathy. The patients with uveitis sometimes complained of blurred vision. Occasionally there was slight enlargement of the blindspots.

#### DIFFERENTIAL DIAGNOSIS

The retinopathy of scrub typhus must be differentiated from papilledema and optic neuritis, as well as from the retinopathy of renal and hypertensive vascular disease. Papilledema due to increased intracranial pressure was definitely excluded by the study of cerebrospinal fluid pressures. Lumbar punctures were made on 16 patients with changes in the eyegrounds. Slight or moderate elevation of pressure was found in only 5 of these patients, and this usually in association with an increase in the cell count and protein content. Lumbar punctures were made on 8 patients with normal eyegrounds, 2 of whom had increased cerebrospinal fluid pressures. These observations show that although in occasional in-

stances the increased cerebrospinal fluid pressure may contribute to the edema of the disk it is not the underlying cause. Additional points of value in excluding papilledema are the vascular changes and the diffuse edema of the retina seen in the retinopathy of scrub typhus. Optic neuritis resembles the retinopathy of scrub typhus but was ruled out by the absence of visual disturbances and of a central scotoma. Also, optic neuritis is likely to be unilateral, whereas the retinopathy of scrub typhus is invariably bilateral. The retinopathy of hypertensive vascular and renal

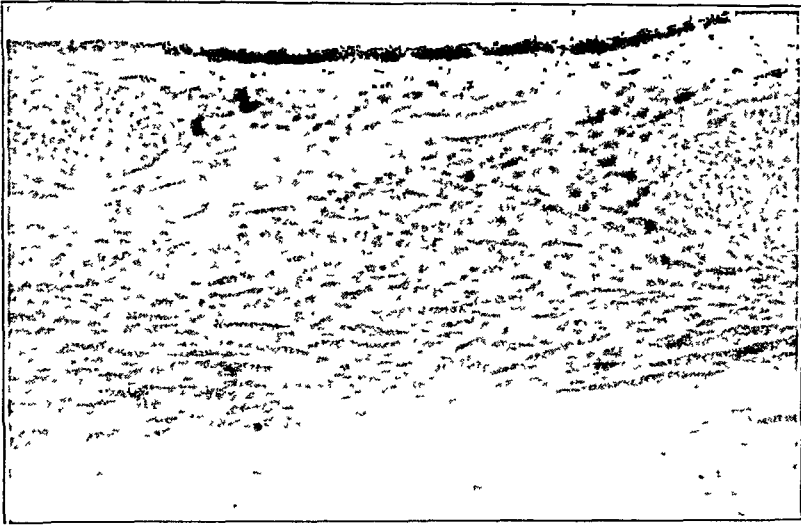


Fig. 8.—Photomicrograph, showing cellular infiltrate in the choroid. Army Institute of Pathology, Washington, D. C.

disease can be differentiated from that of scrub typhus by the characteristic changes in the retinal arteries. Hard, shiny exudates, particularly in the macular region, have not been seen in cases of scrub typhus.

#### OCULAR PATHOLOGIC CHANGES

The eyes of 9 patients were obtained at autopsy for pathologic study. The descriptions of the changes observed in these specimens and their interpretation, as recorded here, were prepared by Dr. Wilfred E. Fry.

These patients were too ill to permit examination with the slit lamp and the corneal microscope. The visual fields could not be taken. None had any visual complaints, nor was any impairment of visual function discovered while the patients were in sufficiently good condition to cooperate in the examination.

#### REPORT OF AUTOPSIES

CASE 1.—W. F., a white soldier, aged 26, died of scrub typhus on the fifteenth day of his illness.

*Ophthalmologic Consultation.*—External Examination: External examination did not reveal anything significant.

Ophthalmoscopic Examination: Right eye: The media were clear. The outlines of the disk were slightly blurred. There was no evidence of edema. The optic nerve was normal. The retinal veins were engorged. No hemorrhages or exudates were present.

Left Eye: The picture was similar to that of the right eye.

*Pathologic Report.*—Cornea: The cornea was normal except for loss of the epithelium. There was no indication of edema, ulceration or necrosis.

Anterior Chamber: The angles were open. No exudates were present.

Iris and Ciliary Body: The iris showed no infiltration. The ciliary body was slightly infiltrated with mononuclear cells. No hyperemia of either the iris or the ciliary body was noted.

Lens: The lens was normal.

Choroid: The choroid was thicker than normal, with dilated vessels and considerable infiltration with mononuclear cells (fig. 8). No epithelioid or giant cells were present.

Retina: The vessels were dilated. No subretinal exudate or retinal hemorrhage was seen.

Optic Nerve: The disk did not appear edematous. No cellular infiltration was noted. The subarachnoid space was moderately dilated.

Sclera: The sclera was normal.

*Impression.*—The pathologic changes in this eye consisted in diffuse subacute choroiditis with possible slight involvement of the ciliary body.

CASE 2.—J. C., a white soldier, aged 22, died of scrub typhus on the fifteenth day of his illness.

*Ophthalmologic Consultation.*—External Examination: Conjunctival hyperemia was rather intense.

Ophthalmoscopic examinations were made on the tenth and thirteenth days of his illness, and one-half hour before his death. On the tenth day the outlines of the disk were blurred in each eye. The veins were greatly engorged and appeared compressed at the arteriovenous crossings. On the thirteenth day of the illness definite edema of the disks and retina was noted. Retinal folds parallel with the disk were seen temporally in each eye. Examination one-half hour before his death revealed more pronounced edema of the disks and retina, the swelling of the disks measuring 1.5 D. A superficial retinal hemorrhage had appeared along the inferior temporal vessels, about 1 disk diameter from the disk.

*Pathologic Reports.*—Cornea: No abnormal changes were seen. There was partial loss of epithelium, but this was probably an artefact, due to injury in fixation and handling.

Anterior Chamber: The angles were open. In one angle was a small collection of mononuclear cells, some of which contained pigment granules.

Iris and Ciliary Body: Both structures were normal in appearance. No inflammatory changes or hyperemia was present. No posterior synechiae were seen.

Lens: The appearance did not suggest cataract.

Choroid: The choroid appeared one-third to one-half thicker than usual. Many of the vessels were dilated. Some were packed with red cells. At one point there were many red cells in the tissue. A mononuclear cell infiltrate, denser near the posterior pole, was present. Near the periphery there were foci of mononuclear cells.

Sclera: The sclera was normal.

**Retina:** The retina was detached; this change was probably an artefact. The retina showed no abnormal changes except for dilated vessels.

**Optic Nerve:** The disk appeared moderately swollen and edematous (fig. 9), with retention of the physiologic cup and no infiltration. The subarachnoid space was dilated.

*Impression.*—The appearance of the disk was that of papilledema. There was an associated severe, subacute, diffuse choroiditis.

**CASE 3.**—L. P., a white soldier aged 24, died of scrub typhus on the fifteenth day of his illness.

*Ophthalmologic Consultation.*—**External Examination:** Ecchymosis had occurred into the right upper lid. Subconjunctival hemorrhages were seen above and temporal to the limbus in each eye.

**Ophthalmoscopic Examination:** The last ophthalmoscopic examination, made two days before death, revealed clear media. Edema of each disk, measuring 1 D.,

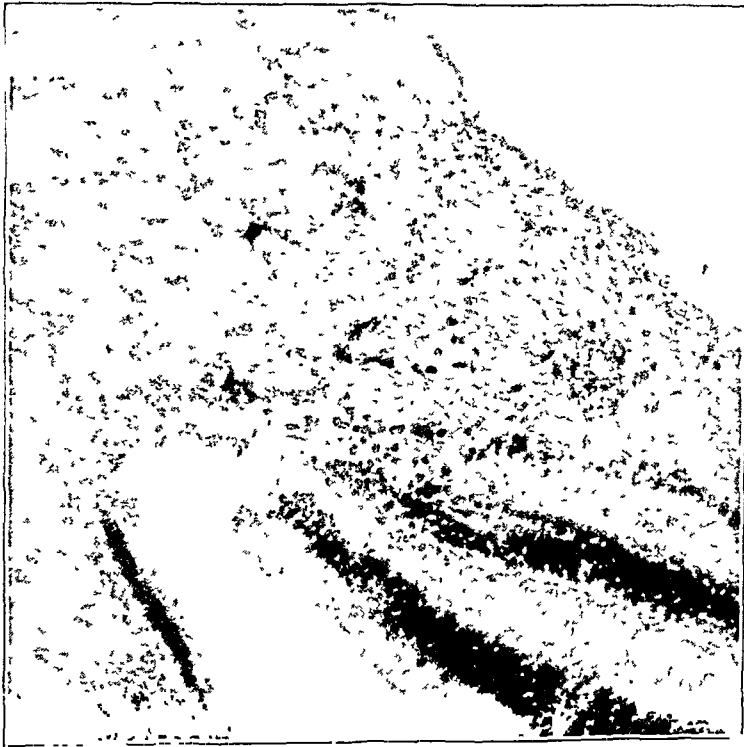


Fig. 9.—Photomicrograph, showing edema of the disk. Army Institute of Pathology, Washington, D. C.

was associated with edema of the retina. The disks were engorged and appeared veiled at the crossings. No hemorrhage or exudate was seen.

*Pathologic Report.*—**Cornea:** The epithelium was partly lost. There were no changes in Bowman's membrane, the stroma, Descemet's membrane or the endothelium. No keratic precipitates were observed. A subconjunctival hemorrhage lay near the limbus at one side.

**Anterior Chamber:** The angles were open. There was no exudate.

**Iris and Ciliary Body:** There was no infiltration or hyperemia. No posterior synechiae were seen.

**Lens:** The lens was normal.

**Choroid:** The choroid was thickened, and there was a diffuse mononuclear cell infiltration, with a sprinkling of large mononuclear cells. The vessels were engorged. No epithelioid or giant cells were seen.

**Retina:** The retina was detached. There were several dilated vessels. No subretinal exudate was seen.

**Optic Nerve:** The disk was edematous. Moderate dilatation of the subarachnoid space with some proliferation of the cells of the arachnoid was noted.

*Impression.*—Severe, subacute, diffuse choroiditis was present in each eye.

**CASE 4.**—T. B., a white soldier aged 34, died of scrub typhus on the sixteenth day of his illness.

*Ophthalmologic Consultation.*—External Examination: No abnormality was found except for an area of ecchymosis involving the right upper lid.

**Ophthalmoscopic Examination:** At the last examination, performed four days before his death, the media were clear; no edema of either disk or the retina could be seen in either eye; the veins were engorged, and no hemorrhage or exudate was present.

*Pathologic Report.*—Cornea: The epithelium was of uniform thickness and regular. Bowman's membrane was present and was uniform in appearance. The stroma fibers were regular and the nuclei normal in distribution and appearance. Descemet's membrane and the endothelium were intact. There were no keratic precipitates.

**Anterior Chamber:** The angles were open. There were no exudates.

**Iris and Ciliary Body:** There was no infiltration or edema, and no synechia was seen. Vascularity was not increased.

**Lens:** The lens was normal.

**Retina:** The retina was detached. Near the disk was a small subretinal exudate. There was no cellular infiltration or hemorrhage.

**Choroid:** A diffuse mononuclear cell infiltration involved nearly the entire choroid. The infiltration was slightly denser in the posterior third, and near the anterior portion several foci of infiltrates were noted. The vessels of the middle zone appeared dilated. No epithelioid or giant cells were seen.

**Optic Nerve:** About one-half the disk showed separation of the fibers suggesting edema. No other changes were noted.

**Sclera:** The sclera was normal.

*Impression.*—The pathologic diagnosis was moderately severe, subacute, diffuse choroiditis.

**CASE 5.**—W. L., a white soldier aged 28, died of scrub typhus on the twenty-second day of his illness.

*Ophthalmologic Consultation.*—External Examination: A subconjunctival hemorrhage was present above the limbus on the left eye.

**Ophthalmoscopic Examination:** Ophthalmoscopic examinations were carried out on six occasions, the last about one hour before death. At the time of the first examination, on the eleventh day of his illness, the only abnormality noted was moderate venous engorgement. The disks were slightly blurred at their poles. These changes progressed, until on the sixteenth day of his illness definite edema of the disk and macula was present bilaterally, and the venous changes were more prominent, the crossings being almost obscured and their outlines hazy in places. By the nineteenth day of his disease a dense preretinal hemorrhage,  $\frac{1}{2}$  disk diameter, had developed midway between and slightly below the disk and macula in the right eye. He also had a similar, but smaller hemorrhage in the macular area (fig. 10). The veins were tremendously engorged, appearing sausage like. One hour before



his death, examination revealed another hemorrhage in the right eye along the inferior temporal vessels, about  $1\frac{1}{2}$  disk diameters from the disk.

*Pathologic Report.*—Cornea: The cornea was normal.

Anterior Chamber: The angles were open, and there were no exudates.

Iris and Ciliary Body: There was no infiltration or hyperemia, and no posterior synechia was present.

Lens: The lens was normal.

Choroid: A mild, diffuse mononuclear cell infiltration was present. Over the posterior pole, on the temporal side of the disk, the vessels were conspicuously dilated.



Fig. 10.—Preretinal hemorrhage in the macular region. *A*, low power; *B*, high power. Army Institute of Pathology, Washington, D. C.

Retina: The retina was detached, and there was no infiltration. A small hemorrhage was present in the retina near the macula.

Optic Nerve: One-half the disk was more prominent than normal, the fibers being separated as by slight edema and forced laterally under the adjacent retina. Physiologic excavation was present, the cup containing several mononuclear cells. The subarachnoid space was not dilated.

*Impression.*—The pathologic diagnosis was mild, subacute diffuse choroiditis with choroidal hyperemia. The changes in the disk suggested early papilledema.

CASE 6.—E. L., a white soldier aged 22, died of scrub typhus on the twentieth day of his illness.

*Ophthalmologic Consultation.*—External Examination: A massive subconjunctival hemorrhage had occurred temporally in each eye.

*Ophthalmoscopic Examination:* The only abnormality found on repeated examinations during the last two days before his death was moderate venous engorgement.

*Pathologic Report.*—Cornea: Most of the surface epithelium was lost, but the rest of the cornea appeared normal. There was no indication of ulceration. Keratic precipitates were not present.

Anterior Chamber: There was no exudate, and the angles were open.

Iris and Ciliary Body: There was no infiltration, edema or hyperemia, and no posterior synechia was noted. The pupils were dilated.

Lens: The lens was normal.

Choroid: There was dilatation of the vessels, chiefly of the middle layer, and involving approximately the posterior half of the globe. There were no cellular infiltrates.

Retina: The retinal detachment which was present was probably an artefact. No exudate or hemorrhage was seen. The vessels were slightly more prominent than usual.

Optic Nerve: The disk appeared normal. However, the vessels were dilated. The subarachnoid space was dilated.

*Impression.*—Hyperemia of the choroid and of the papilla was present.

CASE 7.—J. B., a white soldier aged 51, died of scrub typhus on the fifteenth day of his illness with an overwhelming infection.

*Ophthalmologic Consultation.*—External Examination: The conjunctivas were hyperemic. A massive subconjunctival hemorrhage was observed on the upper half of each eyeball.

*Ophthalmoscopic Examination:* Examination two days before death revealed only moderate venous engorgement.

*Pathologic Report.*—Cornea: No areas of infiltration or ulceration or keratic precipitates were seen.

Anterior Chamber: The angles were open. No exudate was present.

Iris and Ciliary Body: No infiltration or hyperemia was noted.

Lens: A patch of pigment was present on the anterior capsule of the lens, probably resulting from a posterior synechia that had been freed.

Choroid: The choroid was thicker than normal. The vessels were dilated. There was moderate mononuclear cell infiltration. The infiltration extended nearly to the ciliary body and, in the more anterior parts of the choroid, tended to occur in foci.

Retina: The retinal detachment which was present was an artefact. The vessels near the disk were moderately dilated.

Optic Nerve: There was no edema of the disk. There was moderate proliferation of the cells of the arachnoid; in addition, a number of mononuclear cells had infiltrated in from the subarachnoid space. The subarachnoid space was dilated.

*Impression.*—The diagnosis was moderate subacute, diffuse choroiditis and subacute perineuritis.

CASE 8.—E. K., a white soldier aged 23, died of scrub typhus on the thirteenth day of his illness.

*Ophthalmologic Consultation.*—External Examination: Mild conjunctival hyperemia was present in each eye.

**Ophthalmoscopic Examination:** The last examination, made five days before his death, revealed blurring of the outlines of the disks, with no definite evidence of edema. The veins were engorged.

**Pathologic Report.**—Cornea: There was partial loss of epithelium, probably an artefact. Bowman's membrane was intact at one point, where there was a small infiltrate. The stroma was normal except for a small area of connective tissue near the center of the anterior surface. Descemet's membrane and the endothelium were intact.

**Anterior Chamber:** The angles were open. There were no exudates.

**Iris and Ciliary Body:** There was no area of infiltration or hyperemia, and no posterior synechia was noted.

**Lens:** The lens was noncataractous.

**Choroid:** The choroid was thicker and more cellular than normal. There was a moderate diffuse mononuclear cell infiltrate of all the posterior half of the choroid.

**Retina:** The usual layers were present. There was no area of infiltration. Near the disk the veins appeared dilated, and at one point a hemorrhage in the fiber and internal nuclear layer was seen.

**Optic Nerve:** The fibers of the nerve at the disk were edematous. Physiologic cupping was preserved. There were no cellular infiltrates about the intact vessels.

**Impression.**—The changes in the disk were those of moderate papilledema. The choroid showed moderate subacute diffuse choroiditis.

**CASE 9.**—J. M., a white soldier, aged 22, died of scrub typhus on the eleventh day of his illness.

**Ophthalmologic Consultations.**—External Examination: No abnormality was found.

**Ophthalmoscopic Examination:** The last examination, done within twenty-four hours of the patient's death, revealed only venous engorgement.

**Pathologic Report.**—Cornea: There was partial loss of the surface epithelium, probably an artefact. Bowman's membrane was intact. The stroma appeared normal. There were no changes in Descemet's membrane or in the endothelium and no keratic precipitates.

**Anterior Chamber:** The angles were open. There was no exudate.

**Iris and Ciliary Body:** There was no infiltration or hyperemia. The pupil was dilated. There was no posterior synechia.

**Lens:** The lens was normal.

**Choroid:** The choroid was thicker than normal. The vessels were dilated. There was a diffuse infiltration, consisting chiefly of small mononuclear cells. There were no epithelioid or giant cells. All the changes were more prominent in the posterior half.

**Retina:** The retinal detachment which was present was probably an artefact. There was no exudate or hemorrhage. Several of the vessels were dilated and filled with red cells. There was no subretinal exudate.

**Optic Nerve:** The fibers of the disk showed questionable edema. There were no other changes.

**Impression.**—The impression was that of mild subacute diffuse choroiditis.

The pathologic changes, therefore, consisted predominantly of posterior chroiditis, manifested by mononuclear cell infiltration. The edema of the disk and engorgement of the retinal vessels seen clinically were confirmed by the pathologic studies. This condition was comparable to

the infiltrative changes elsewhere in the body. Dr. Algernon B. Reese and Dr. Jonas Friedenwald also examined the slides and were in general agreement with the observations as recorded. Dr. Friedenwald,<sup>9</sup> however, stated the opinion that the choroidal changes might be compatible with the so-called septic choroiditis described by him in 1930 in patients dying of septicemia. After reviewing some of his original slides, he was less inclined to this opinion. The eyes of these patients who had died of scrub typhus showed a considerably more intense and diffuse infiltration of the choroid than did the ones of which he had written.

Dr. Henry Pinkerton, who has worked extensively with rickettsial diseases, studied sections from all these eyes for evidence of rickettsial inclusion bodies but found none. In a personal communication, he stated that from the general pathologic point of view there was definite evidence of vasculitis and perivasculitis. He expressed the belief that there was proliferation of the capillary endothelium. These changes have been described as occurring in other tissues of the body in scrub typhus (Kouwenaar,<sup>10</sup> Lewthwaite, Corbett<sup>11</sup> and the *United States War Department Technical Bulletin*<sup>12</sup>).

These pathologic changes adequately explain the ophthalmoscopic changes of engorged retinal vessels, edema of the disk and retina and opacities in the vitreous. It is also not surprising that the anterior uveal tract is involved in some patients, resulting in ciliary flush and photophobia.

#### CLINICAL RELATION

The relation of the ocular abnormalities to other aspects of scrub typhus was studied in the second group of patients (159). The ophthalmic findings were correlated with data on the severity of the general symptoms and the occurrence of complications. These data were collected and organized by Sayen, Pond, Forrester and Wood as a part of their clinical report on scrub typhus in this hospital.

#### EXTRAOCULAR CHANGES

Subconjunctival hemorrhages late in the first week of the disease were frequently of diagnostic help, since they were uncommon and not so massive in the case of other diseases encountered in this area. Conjunctivitis was less specific but was occasionally helpful.

9. Friedenwald, J. S., and Rones, B.: Some Ocular Lesions in Septicemia, *Tr. Am. Ophth. Soc.* 28:286, 1930.

10. Kouwenaar, W.: Investigations on Rickettsial Diseases in Sumatra, *Geneesk. tijdschr. v. Nederl.-Indië* 80:1119 (April 30) 1940.

11. Corbett, A. J.: Scrub Typhus, *Bull. U. S. Army M. Dept.*, November 1943, no. 70, p. 34.

12. Scrub Typhus Fever, United States War Department, Technical Bulletin (T B. Med. 31), Washington, D. C., Government Printing Office, April 11, 1944.

## INTRAOCULAR CHANGES

The most significant points in the relation of retinopathy to the general clinical picture of scrub typhus may be summarized as follows:

*Type of Onset.*—There was no correlation between the subsequent development of retinopathy and the presence of external ocular signs, ocular pain or photophobia, or the frequency of primary ulcers, rashes or lymphadenopathy.

*Diagnosis.*—The diagnosis of scrub typhus in a case of febrile disease rests on the presence of the ulcer at the site of the mite bite, the appearance of the rash and the presence of increased generalized lymphadenopathy. Later confirmation is provided by the titer of *P. vulgaris* O X K. The incidences of various diagnostic criteria were essentially as follows:

	Percentage
Primary ulcer .....	60
Rash .....	71
Lymphadenopathy .....	97
Agglutination of <i>P. vulgaris</i> O X K .....	63
(In titer of 1:100 or more)	

Thus, in a significant number of cases one or more of the criteria "essential" for early diagnosis were absent. In these clinically atypical cases the development of changes in the eyegrounds was of considerable diagnostic aid, because the retinopathy of scrub typhus was practically pathognomonic, at least in this geographic area. Similar changes are not known to occur in other acute febrile diseases. Cases of malaria, including the cerebral form, typhoid, meningitis and pneumonia have been personally observed, with no comparable retinal changes. Retinopathy develops on an average of three to four days before the agglutination reaction against *P. vulgaris* O X K becomes positive, thus affording diagnostic help before laboratory evidence is available. Thus, in several cases of undiagnosed fevers, the ophthalmologic findings first suggested scrub typhus. In a number of other cases in which scrub typhus was suspected, but not proved until later, the retinal findings helped to clinch the diagnosis.

*Severity of Disease.*—The distribution of the patients with and without retinopathy among the various groups into which this series was divided on the basis of clinical severity is shown in table 1. It can be

TABLE 1.—*Distribution of Cases of Scrub Typhus with and Without Retinopathy According to Clinical Severity*

	Group 1 Mild (48)	Group 2 Moderately Severe (48)	Group 3 Severe (33)	Group 4 Grave (18)	Group 5 Total (12)
Retinopathy .....	8	17	21	16	5
Normal fundi .....	40	31	12	2	7

seen that there is a definite increase in the frequency of retinopathy as the disease increases in severity (fig. 11). The lower incidence of retino-

pathy recorded in the fatal cases than in the cases of the severe and grave forms is probably attributable to the fact that death interrupted the development of the retinal lesion.

*Complications.*—Although wide dissemination of the rickettsial disease process is the rule, certain patients exhibited clearcut signs of dam-

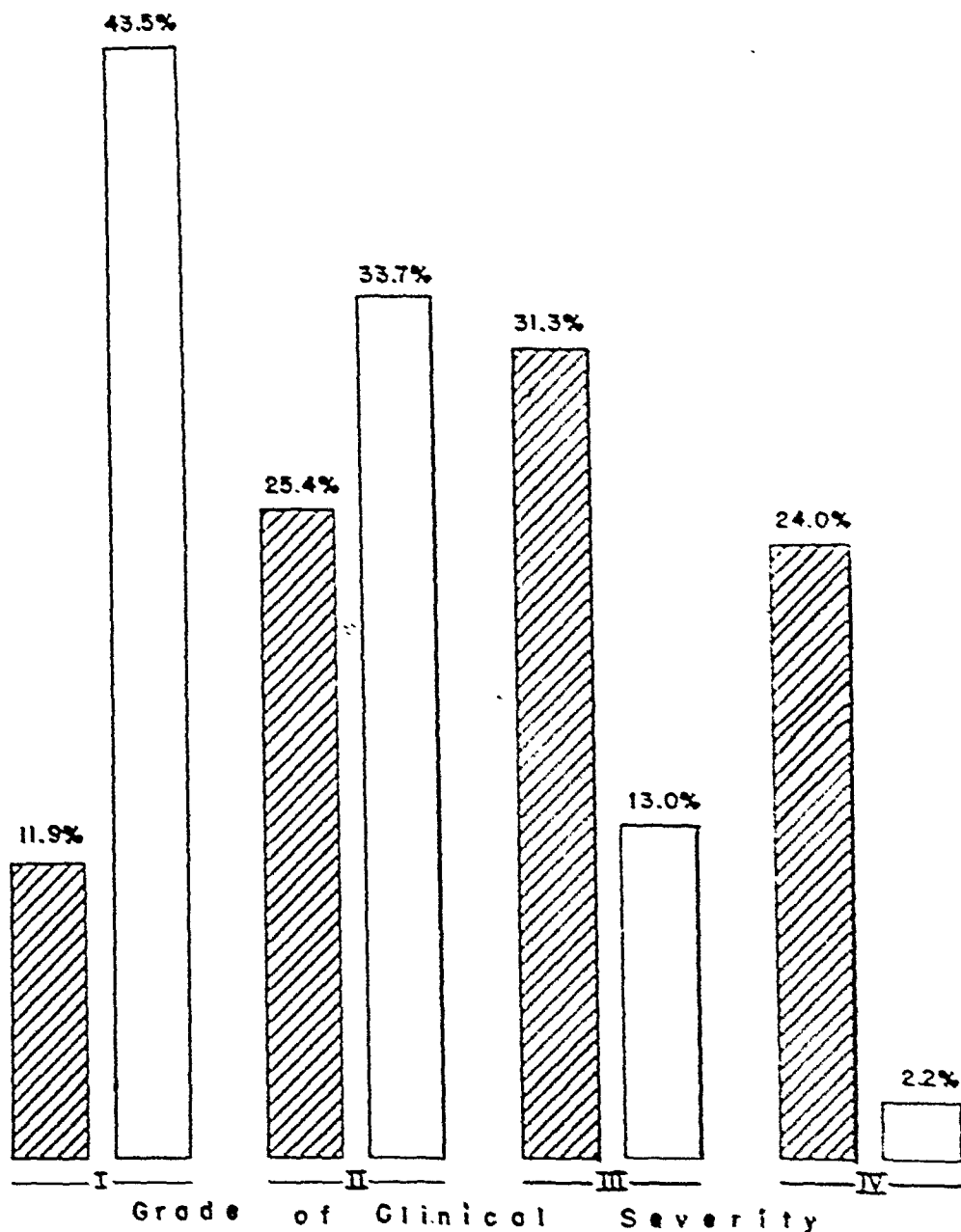


Fig. 11.—Relation of retinopathy to severity of the disease in patients with scrub typhus. The cross hatched areas represent patients with retinopathy; the clear areas, those without retinopathy. Army Institute of Pathology, Washington, D. C.

age to parenchymal organs, while others did not. Clinical and pathologic analysis of 159 cases and the hospital's experience in general demonstrated that extensive damage to important organs was largely confined to the

severely ill patients and that it played a major part in the outcome of the disease. When the following clinical signs appeared, a complication was said to be present, although the term is not thoroughly satisfactory:

Complication	Clinical Sign
Meningitis .....	Stiff neck
Encephalitis.....	Extreme restlessness, delirium, convulsions or coma
Myocarditis.....	Definite cardiac enlargement or pronounced electrocardiographic changes
Interstitial pneumonia.....	Cyanosis and greatly increased respiratory rate
Hepatitis .....	Jaundice
Interstitial nephritis.....	Albuminuria and granular casts, associated with decreased urinary volume, isosthenuria or uremia
Abnormal fluid balance.....	Edema and ascites

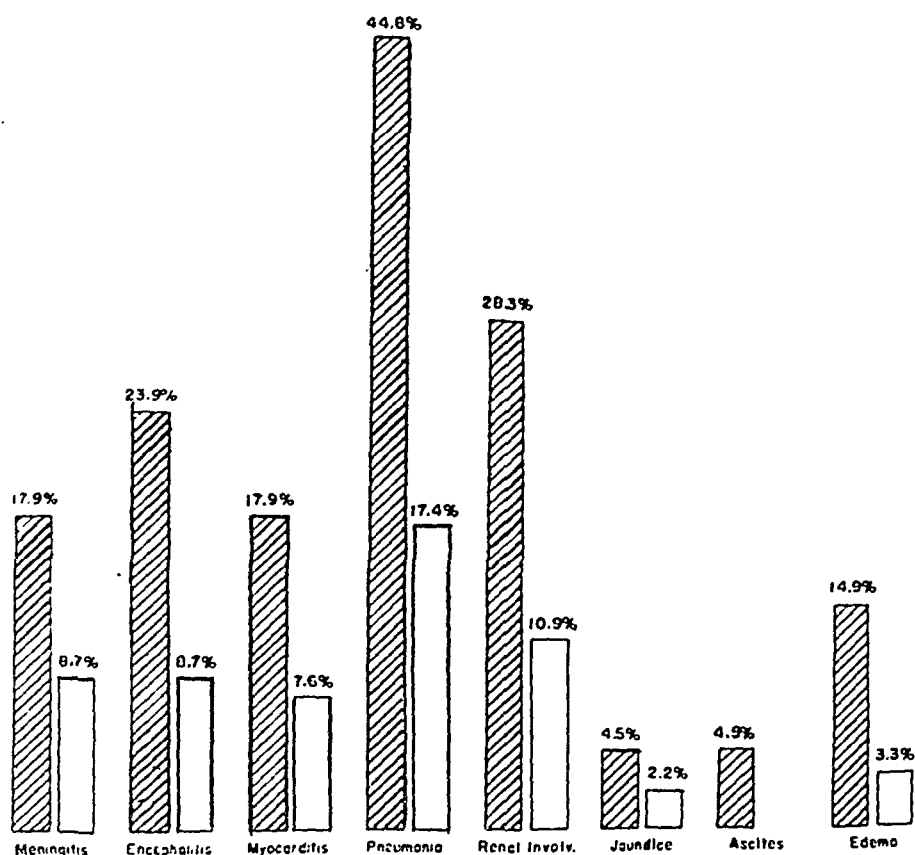


Fig. 12.—Relation of retinopathy to complications in patients with scrub typhus. Patients with retinopathy are represented by the cross hatched areas; those without retinopathy, by the plain areas. Army Institute of Pathology Washington, D. C.

There is a significant correlation between the incidence of these complications and that of retinopathy. A large number, 45 (67.2 per cent), of the 67 patients who had changes in the eyegrounds exhibited one or more complications. Conversely, such complications occurred in only 31 (33.7 per cent) of the patients with normal fundi. The incidence of complications in patients with and without retinopathy is illustrated in table 2 and is compared on a percentage basis in figure 12.

*Convalescence.*—One of the major problems in the management of convalescence from scrub typhus is to know how soon the patient has fully recovered. One can, as a rule, estimate the time fairly well on the basis of the general condition of the patient. In a patient with retinopathy, the time of disappearance of the retinal lesion furnished an additional objective criterion of recovery. It is reasonable to suspect that the disappearance of retinal changes parallels the disappearance of damage elsewhere. Consequently, no patient was returned to duty before his retinopathy had disappeared.

TABLE 2.—*Incidence of Complications in Patients with Scrub Typhus with and Without Retinopathy*

	Menin- gitis (20)	Enceph- alitis (24)	Myocar- ditis (19)	Pneu- monia (46)	Jaun- dice (5)	Neph- ritis (29)	Edema (13)	Ascites (3)
Retinopathy .....	12	16	12	30	3	19	10	3
Normal fundi .....	8	8	7	16	2	10	3	0

#### SUMMARY

The eyes of 451 patients with scrub typhus were studied weekly for evidence of disease. The following external changes were seen: (1) conjunctival injection, 38 per cent; (2) subconjunctival hemorrhages, 6.4 per cent; (3) ecchymosis of the eyelids, 1.0 per cent; (4) eschar on the eyelid, 0.5 per cent; (5) fixation nystagmus, 0.5 per cent.

The following ocular changes were seen: (1) engorgement of veins, 67 per cent; (2) retinal edema, 36 per cent; (3) retinal hemorrhages, 6.6 per cent; (4) exudates, 4.9 per cent; (5) uveitis, 1.3 per cent; (6) vitreous opacities, 4.6 per cent.

Pathologic studies of eyes obtained at autopsy revealed that a sub-acute diffuse choroiditis was the basic lesion. Since changes in the fundus of this type had not been seen in other febrile diseases in this area, their presence was frequently helpful in diagnosis.

Since its disappearance presumably occurs at about the time of recovery from other parenchymal lesions of scrub typhus, it was used as a criterion for the stage of convalescence.

Lieut. Margaret Kabatt, Technician Third Class James A. Bergan and the entire staff of the eye, ear, nose and throat clinic aided in maintaining the records and in compiling the data in preparing this paper. Capt. Graham Eddy and the First Medical Museum and Arts Detachment furnished the illustrations.

313 South Seventeenth Street.



## NEARLY ONE HUNDRED YEARS OF THE OPHTHALMOSCOPE

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NO INSTRUMENT in general medicine has influenced and developed a specialty as the ophthalmoscope has done for ophthalmology. In addition, the ophthalmoscope has been of importance in other branches of medicine, as it stimulated the development of instruments for examination of other parts of the body, such as laryngoscopy, rhinoscopy, gastroenteroscopy and cystoscopy. In this connection, it should be stated that the exact date of the discovery of these methods cannot be given. A report of the conditions which led to the discovery of the ophthalmoscope may be of interest to those less informed, and its publication is timely in view of the centenary of the day when von Helmholtz presented his discovery before the Physical Society in Berlin, on Dec. 16, 1850. There is no question in my mind that the sturdy ophthalmoscope will survive its one-hundredth birthday, a prospect which is not necessarily applicable to my own case, so that I have decided to write this report somewhat ahead of time.

Before entering on a discussion of the discovery of the ophthalmoscope, I wish to say a few words about von Helmholtz as a person. Von Helmholtz' life has been so admirably described in the monumental work of Königsberger<sup>1</sup> that I have taken much of the following account from this book. Von Helmholtz was born on Aug. 31, 1821, in Potsdam, the son and first child of a high school teacher, Ferdinand Helmholtz, who was then 30 years old. The boy was named Hermann Ludwig Ferdinand; he was a delicate child, passing the first seven years of his life principally indoors on account of illness, and mostly in bed, devoting himself to picture books, and especially to building blocks. During this period he received every encouragement on the part of his parents, who were much concerned about his mental development. In his seventh year his schooling began, but it was often interrupted by illness. He astonished his teachers by his grasp of geometry, which is ascribed to his playing with blocks. On the other hand, he was less successful in studies in which memory was a feature. Many years later he remembered how difficult

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1. Königsberger, L.: Hermann von Helmholtz, Braunschweig, F. Vieweg & Sohn, 1902.

it was for him to learn by heart vocabularies, grammatical rules and connected prose. After finishing high school, he wanted to begin the study of natural science, but this his father's means did not permit, as the family now consisted of five children. It was finally arranged that the eager youth should take up mathematics and physics in connection with his early studies in medicine. After passing the examination, he obtained a preliminary scholarship in the Royal Medico-Surgical Friedrich-Wilhelm Institute. In consideration of certain conditions, he was allowed board and lodging during the years of his medical education at the University of Berlin, with the obligation that he serve in the army as physician for seven years after graduation. Von Helmholtz remained at this school from 1838 to 1842; as assistant in the library, he had access to mathematical textbooks, which, with intensive study in mathematics and physics, enabled him to do independent work and eventually to become, even at an early age, one of the celebrated mathematicians of his day.

He was most attracted to the physiologist Johannes Müller, of the medical faculty, as were his fellow students and intimates, Brücke, Dubois-Reymond and Ludwig, among whom a friendly and most active intellectual relationship existed. This was the period when great development was taking place in chemistry and mathematics, and mention need only be made of Lavoisier, Liebig, Coulomb, Ohm and, especially, Ernst Heinrich Weber. The last insisted on tracing back both the vital and the nonvital forces to physicochemical processes, independent of the mystic conception of life. Von Helmholtz held firmly to these views.

With a small microscope, which he purchased with his savings, he discovered the nerve fibers which arise from ganglion cells (discovered by Ehrenberg) and recognized their central origin, thus laying the histologic basis of all physiologic and pathologic processes in nerves.

This investigation, which particularly impressed Johannes Müller, was Helmholtz' doctor's dissertation, presented on Nov. 2, 1842. He then began his term as military physician, which lasted from 1843 to 1848. He performed his military duties with full conscientiousness and prepared himself for additional medical examinations, at the same time finding time for scientific work. He was occupied with the experimental investigation of a number of problems, especially those on fermentation and putrefaction, the nature of which he recognized as not being purely chemical, but vital as well, thus anticipating the ideas of Pasteur. Then the question of the origin of heat interested him greatly, and he recognized its important source in muscular action. He began the study of frog's muscles by means of a self-constructed electrical apparatus and determined the propagation of a nerve stimulus with methods which measured the smallest time intervals. All these investigations pointed to

a close interrelationship (von Helmholtz had grown to consider the idea of a vital force as a paradox and had arrived at the concept that neither energy nor matter can disappear). He therefore approached the problem of the preservation of energy at the same time that Robert Meyer and Joule came to the same conclusion by other lines of investigation. This subject was the title of an address which he delivered on July 23, 1847, before the Society of Physics; this paper was not accepted for publication in Poggendorf's annals because the article, in the editor's opinion, was speculative and without the experimental basis on which articles in this journal were supposed to depend. His friend, DuBois-Reymond, was disturbed by this rejection, and, on his suggestion, von Helmholtz published the article separately, with the preface by DuBois, in which he stated that it contained a program for modern natural science.

Though von Helmholtz had gained high esteem in scientific circles by his investigations, it was the discovery of the ophthalmoscope which made him famous throughout the world and connected his name for all time with this marvelous instrument.

This discovery took place, curiously, without any previous investigations or experiments bearing on this problem. As professor of physiology in Königsberg, and successor to Brücke, he demonstrated the lighting up of the pupil when light was projected into the eye with a mirror, an observation which had long been known. He expressed the belief that the rays of light which were returned from the eyeground must furnish a picture of this structure. If a convex lens was held between the observer and the observed in the course of the light rays, an inverted picture resulted, while if the observer came close to the observed the rays of light as they emerged from the eye produced a direct image of the eyeground. Thus, the discovery of the ophthalmoscope was based on many previous observations on the illumination of the pupil. I was not able to determine who was the first to observe the phenomenon of illumination of the pupil; without question, this was the most important observation which preceded the discovery of the ophthalmoscope and, in fact, contained the germ of the discovery.

The first presentation of von Helmholtz' discovery took place before the Physical Society of Berlin on Dec. 6, 1850. On December 7 von Helmholtz wrote the following letter to his father:

On the occasion of my lectures on the physiology of the sense organs, I made a discovery which may be of real value to ophthalmology; it was so simple, requiring no more knowledge than what I had learned of optics in high school, that it is laughable that other people and I could have been so obtuse as not to have recognized it before.

A combination of lenses is necessary to illuminate the dark background of the eye through the pupil without using a dazzling light; then all the details can be seen more clearly than one sees the exterior of the

eye without magnification, because the transparent parts of the eye act in place of a loupe with a magnification of 20. The retinal blood vessels, arteries and veins, as well as the optic nerve, can be identified in their smallest branches. These were the words which revealed von Helmholtz' rapture as the first observer of the eyeground, a rapture which is shared by every one who observes for the first time the beautiful picture of the fundus with the miraculous aid of the ophthalmoscope. The letter continues:

Formerly, a number of ocular diseases were designated under the term "black cataract," an unknown field, as the changes in the living and in the dead eye were not understood. My discovery permits the most specialized examination of the internal parts of the eye.

This statement shows that von Helmholtz, with the greatest modesty, regarded his findings as a scientific contribution—an observation rather than a discovery—but that from the first he was impressed with its practical importance. He added that he proclaimed before the Physical Society of Berlin that the instrument was like "Columbus' egg, which is to be most carefully treated." He went on to say that a more practical and improved model than the *papier maché* contrivance was being manufactured and that examinations by the head ophthalmologist in Berlin were then to be made and reported later.

His great contemporary, von Graefe, was equally impressed with the practical importance of the ophthalmoscope, and in the later years opened up new fields in ophthalmology with this instrument. Von Graefe wrote to von Helmholtz on Nov. 7, 1861, as follows:

My dear Professor: Forgive me as one not known to you for addressing this letter to you, to ask you about a subject of the greatest interest to me. Last summer, Professor Brücke, in Vienna, told me that you had succeeded in constructing an instrument which permitted the examination of the living retina. As I have devoted myself to ophthalmology with particular enthusiasm for a number of years, I am anxious to try out this much longed-for diagnostic instrument, to the advantage of science in general. I have promised to forward models to my London and Paris colleagues, Dr. Bowman and Dr. Desmarres. The former, who is most interested in the scientific development of our specialty and has a large service at Moorfields Hospital, is particularly eager to receive an early model. I have asked Dörfel, my local instrument maker, to make the instrument, and I want first to compare it with one which was made in Königsberg under your supervision. I am therefore begging you to ask your mechanic to send to Berlin one or two of the instruments constructed according to your specifications. With the hope that you will pardon my presumption because of my interest in the subject, believe me, yours most truly, Dr. A. von Graefe, physician-operator in Berlin.

In the years following the discovery of the ophthalmoscope, von Helmholtz published his "Optique Physiologique,"<sup>2</sup> and thereby created the theoretic foundation of ophthalmology; this was followed by a series

2. von Helmholtz, H.: *Optique physiologique*, Paris, V. Masson & fils, 1867.

of acoustic, as well as mathematical and physical, investigations and transformed in 1871 the medical von Helmholtz to the highest ranking professor of physics in the University of Berlin, thirty-two years after he had begun his studies in Berlin at the military academy. At this time he was invited to become professor of experimental physics at Cambridge (England), under the most flattering conditions.

One of the more important contributions which he made at this time was to organize and plan the Royal Physico-Technical Institute at Charlottenberg, of which he acted as president up to the date of his death.

With his recognition in all parts of the world, it was natural that he should be elected as a worthy representative of his country and of his university at meetings in foreign countries, such as the Electrical Congress, in Paris, in 1882; the Geodetic Congress, in Rome, in 1883; the celebration of the six hundredth anniversary of the celebrated medical school in Montpellier, in 1890, and the World's Fair in Chicago, in 1893. On every occasion he was received with the greatest enthusiasm.

In Montpellier, he said, speaking of the unifying force of science:

No one of us can work scientifically without aiding his own country, and at the same time the entire civilized world. All nations that work in science have a common field and necessarily help one another. This truth must finally prevail and lead to a friendly relationship in the world.

He concluded that it is medicine which has always practiced this peace-producing habit of science and has presented it before the eyes of the world, even in the moment of the emotional reactions of war.

Julienstrasse 50 (XVIII).

## CHOLINESTERASE IN THE AQUEOUS OF THE EYE

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BROOKLYN

EVER SINCE the discovery of cholinesterase by Loewi and Navratil<sup>1</sup> in 1926, the number of experimental investigations concerning this vital enzyme has been almost legion. Cholinesterase is capable of converting acetylcholine into the relatively inactive choline and acetic acid. Consequently, it represents a new tool in the study of autonomic activities.

In the past twenty-two years the cholinesterase content of well nigh every tissue in the human and lower organisms has been noted. The tissues of the eye have not been neglected. Interestingly enough, it is concerning them that one of the few controversies exists.

Cholinesterase is not a difficult substance to work with. It is relatively stable. Vahlquist<sup>2</sup> stated that blood plasma at room temperature in a sealed tube retains its cholinesterase activity for at least a week. Stedman<sup>3</sup> stated that serum, if sterile, retains its cholinesterase activity for months. Recently, many new methods have been devised for accurate determination of the enzyme.

Considerable importance within recent years has been ascribed to the autonomic nervous system in the genesis of ophthalmic diseases. The possibility that the cause of glaucoma lies in a disturbance in central autonomic pathways has been suggested by Schoenberg. This work is supported by pupillographic records from glaucomatous patients.<sup>4</sup>

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Funds donated by the Jewish Hospital of Brooklyn aided in the performance of this work.

1. Loewi, O., and Navratil, E.: Ueber humorale Uebertragbarkeit der Herznervenwirkung: X. Ueber das Schicksal des Vagusstoffs, *Arch. f. d. ges. Physiol.* **214**:678, 1926.

2. Vahlquist, B.: On Esterase Activity of Human Blood Plasma, *Skandinav. Arch. f. Physiol.* **72**:133, 1935.

3. Stedman, E., and Stedman, E.: Relative Cholinesterase Activities of Serum and Corpuscles from Blood of Certain Species, *Biochem. J.* **29**:2107, 1935.

4. Löwenstein, O., and Schoenberg, M.: Nervous Factor in the Origin of Simple Glaucoma, *Arch. Ophth.* **31**:384 (May) 1944; Pupillary Reactions of the Seemingly Unaffected Eye in Clinically Unilateral Simple Glaucoma: Pupillographic Contributions to the Diagnosis of Glaucoma in the Preclinical Stage, *ibid.* **31**:392 (May) 1944.

More recently, Bloomfield<sup>5</sup> studied the aqueous of normal eyes and observed that the fluid caused an isolated frog heart to decrease its amplitude of contraction. On the contrary, aqueous from the eyes of glaucomatous patients caused a slight increase in the amplitude. He attributed the latter to a parasympathetic deficiency in the aqueous and suggested this as a possible etiologic factor in the causation of glaucoma. Rados<sup>6</sup> studied the blood cholinesterase levels of patients with glaucoma but could find no significant deviations from normal values. Pletneva, Raeva and Veronina<sup>7</sup> examined the aqueous of a large number of patients with glaucoma and of others with cataract. In 52 per cent of the patients the aqueous was sympathicotropic and in 34 per cent vagotropic. Hence, it would seem that the cholinesterase activity of normal and pathologic eyes would be of considerable value in establishing the autonomic genesis of many disorders.

Cholinesterase has been demonstrated in all the tissues of the eye. Herrmann and Friedenwald<sup>8</sup> studied the cholinesterase content of the ciliary processes and the choroid plexus. They showed that these tissues contain considerable cholinesterase, although there is no evidence that the secretory activity of either is cholinergic. Brückner<sup>9</sup> studied the occurrence and distribution of cholinesterase in the uvea. Anfinson<sup>10</sup> showed its occurrence in the retina, and Weve and Fischer<sup>11</sup> demonstrated cholinesterase in the subretinal fluid in cases of detached retina. The vitreous has been shown by many to contain cholinesterase. This work has been done by many, and no controversy has existed. However, there has been a dispute over the cholinesterase content of the aqueous.

In 1930, Plattner and Hintner,<sup>12</sup> working on cats, demonstrated the presence of cholinesterase in the aqueous. Velhagen,<sup>13</sup> in work done from

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5. Bloomfield, S.: Relative Deficiency of Parasympathetic Activity in Aqueous of Eyes with Chronic Simple Glaucoma, *Arch. Ophth.* **37**:608 (May) 1947.

6. Rados, A.: Blood Cholinesterase Values of Patients with Glaucoma, *Arch. Ophth.* **30**:371 (Sept.) 1943.

7. Pletneva, N.; Raeva, N., and Veronina, E.: Biologic Analysis of Aqueous Humor in Glaucomatous Patients, *Vestnik oftal.* **13**:462, 1938.

8. Herrmann, H., and Friedenwald, J. S.: Cholinesterase Content of Choroid Plexus and Ciliary Processes, *Bull. Johns Hopkins Hosp.* **70**:14, 1942.

9. Brückner, R.: Auge und Cholinesterase: Vorkommen und Verteilung von Cholinesterase in der Uvea, *Ophthalmologica* **106**:200, 1943.

10. Anfinson, C. B.: Distribution of Cholinesterase in Bovine Retina, *J. Biol. Chem.* **152**:267, 1944.

11. Weve, H. J. M., and Fischer, F. P.: Cholinesterase Content of Subretinal Fluid in Detached Retina, *Ophthalmologica* **96**:348, 1939.

12. Plattner, F., and Hintner, H.: Die Spaltung von Acetylcholin durch Organe und trakte Körperflüssigkeiten, *Arch. f. d. ges. Physiol.* **225**:19, 1930.

13. Velhagen, K.: Ueber die antagonistischen Beziehungen zwischen Hinterlappenhormonen und Insulin, *Arch. f. exper. Path. u. Pharmakol.* **142**:127, 1929;

1929 to 1936, showed also that cholinesterase was present in the normal aqueous. However, the first objection to these findings arose when Uvnäs and Wolff,<sup>14</sup> working on bovine eyes, were unable to demonstrate cholinesterase in the aqueous. To explain this contradiction, they offered the possibility that previous investigators had effected too great an emptying of the anterior chamber of the eye, thus causing seepage of cholinesterase-rich vitreous into the specimen. Brückner,<sup>15</sup> in 1943, working on horses and cows, stated that cholinesterase is a regular component of the aqueous and suggested that the enzyme arises from sources other than the blood. Further, he stated that the aqueous of the horse was richer in cholinesterase than the vitreous.

Before discussing the results of the present work, it might be advantageous to attempt to settle the dispute purely on theoretic grounds, i.e., by what is known of the chemistry of enzymes and of the aqueous.

Northrop<sup>16</sup> showed that enzymes obtained in crystalline form had identical physical properties as crystalline proteins. Previous to this it had been known that enzymes were in some way associated with proteins. However, it was not definitely established whether enzymes were proteins or were linked in some way with proteins. However, Northrop showed that the crystalline enzyme, when devoid of all other protein substances, still had the identical properties of a protein. Bodansky<sup>17</sup> concluded that every enzyme which has thus far been obtained in crystalline form has been a protein.

Further work has shown that the property of an enzyme may be due to a union between a protein group and another large chemical group. That is, many enzymes are conjugated proteins (a protein whose molecule is combined with another, nonprotein, group). A common example of a conjugated protein is hemoglobin (heme plus globin). At any rate, it has been established that every known enzyme is a protein. Cholinesterase has been shown by Engelhart and Loewi<sup>18</sup> to be enzymatic in nature. Consequently, cholinesterase is in all likelihood a protein.

Einleitende Untersuchungen über das Vorkommen aktiver und neurotroper Substanzen im Auge, *Arch. f. Augenh.* **103**:424, 1930; Ueber das Vorkommen depressorischer Substanzen im Auge, *ibid.* **104**:546, 1931; Zur Frage der vagotropen Substanzen im Auge, *ibid.* **105**:573, 1932; Die hypoxämische Farbenasthenopie, eine latente Störung des Farbensinnes, *ibid.* **109**:605, 1936.

14. Uvnäs, B., and Wolff, H.: On Occurrence of Acetylcholine Esterase in Aqueous Humour and Vitreous Body, *Acta ophth.* **16**:157, 1938.

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17. Bodansky, M.: Introduction to Physiological Chemistry, ed. 4, New York, John Wiley & Sons, Inc., 1938, p. 133.

18. Engelhart, E., and Loewi, O.: Fermentative Azetylcholinspaltung im Blut und ihre Hemmung durch Physostigmin, *Arch. f. exper. Path. u. Pharmakol.* **150**:1, 1930.



It is known that the protein content of the normal aqueous is almost nil. According to Duke-Elder,<sup>19</sup> the ratio of the protein in the aqueous to that in serum may be expressed for different animals as follows: horse, 1:370; cow, 1:440; rabbit, 1:140. The proteins in the aqueous are the same as those in the serum of the same animal. In addition, they maintain the same relative proportions in the aqueous and in the blood. The same may be said for immune bodies and for enzymes.

Thus far, two important points have been stated: 1. The protein content of normal aqueous is almost nil. 2. Cholinesterase is an enzyme, and

TABLE 1.—*Cholinesterase Determinations on Normal Aqueous of the Cat\**

Specimen No.	Amount of Aqueous, Cc.	Amount of 0.02 Normal Sodium Hydroxide, Cc.
1	0.7	0.06
2	0.4	0.00
3	0.4	0.05
4	0.75	0.013
5	0.75	0.013
6	0.6	0.00
7	0.7	0.00
8	0.2	0.00
9	0.85	0.00
10	0.8	0.00

\*Results are expressed as the number of cubic centimeters of 0.02 normal sodium hydroxide required to neutralize the acid produced from a 1.2 molar solution of acetylcholine by the test solution. With the method used, the values can be reproduced to  $\pm 0.05$  cc. Therefore, the results indicated in the table show that the normal aqueous of the cat is essentially negative for cholinesterase.

consequently a protein. Therefore, on theoretic grounds, one would not expect to find significant quantities of cholinesterase in the aqueous.

#### PRESENT INVESTIGATION

**EXPERIMENT.—Procedure.**—Ten normal cats were chosen. Less than 1 cc. of aqueous was removed from the right eye of each animal. The paracentesis was performed by direct puncture with a 26 gage needle on a tuberculin syringe. In no case was all the aqueous removed. Cholinesterase determinations were made on all the specimens according to the method to be described. The results are shown in table 1.

**Method of Determination.**—A modified Stedman technic<sup>3</sup> was used. All determinations were made at 37.5 C., at a pH of 7.4 for a period of twenty minutes. The substrate used was a 1.2 molar solution of acetylcholine. The test solution (cholinesterase) was added until the acid liberated by the reaction was neutralized.

19. Duke-Elder, W. S.: Textbook of Ophthalmology, London, Henry Kimpton, 1932, vol. 1, p. 427.

The values are expressed as cubic centimeters of 0.02 normal sodium hydroxide. The average normal value for plasma is 3.33 cc.; that for whole blood, 5.8 cc.

EXPERIMENT 2.—Four normal cats were chosen. From each animal 1 cc. of the aqueous of the right eye was removed and discarded. The second aqueous, which formed within five minutes, was removed and saved (A specimen). The third aqueous from the 4 eyes was then withdrawn and saved (B specimen). Cholinesterase determinations were made on the saved A and B specimens.

The results are shown in table 2.

All A specimens represent the first re-formed aqueous, and all B specimens, the second re-formed aqueous. The average value for the first re-formed aqueous (A) was 0.68 cc.; that for the second re-formed aqueous (B) was 0.92 cc. The average A specimen showed a cholinesterase activity which was about 21 per cent, and the average B specimen an activity which was 28 per cent, of normal plasma cholinesterase.

TABLE 2.—*Cholinesterase Values of Second Aqueous of 4 Cats\**

Specimen No.	Amount of Aqueous, Cc.	Amount of 0.02 Normal Sodium Hydroxide, Cc.
17 A	0.40	0.70
18 A	0.75	0.64
19 A	0.85	0.68
20 A	0.70	0.70
17 B	0.60	0.98
18 B	0.45	0.80
19 B	0.35	0.97
20 B	0.67	0.94

\*The amount of cholinesterase is expressed in cubic centimeters of 0.02 normal sodium hydroxide required to neutralize the acid produced from a 1.2 molar solution of acetylcholine by the test solution.

#### COMMENT

Since cholinesterase is a protein, and since proteins enter the normal aqueous in only minute quantities, one should not expect to find significant amounts of cholinesterase in the normal aqueous.

It is well known that the aqueous which enters the eye after a paracentesis is relatively rich in protein. The protein content of this new aqueous is about 30 per cent of the value for plasma. Since the new aqueous shows a relatively large amount of cholinesterase activity (21 per cent of plasma), it is reasonable to assume that the cholinesterase entered with the protein fraction. Consequently, this is another property which cholinesterase has in common with the proteins of the blood. A second paracentesis of an eye causes a still greater inflow of protein, and therefore the enzyme content increases still further.

In glaucoma, the protein content of the aqueous has never been known to be increased. Consequently, cholinesterase cannot be present in

the aqueous of a glaucomatous eye. This supposition is indirectly supported by the work of Pletneva, Raeva and Veronina,<sup>7</sup> who examined the aqueous of a large number of patients with glaucoma for sympathetic and parasympathetic activity. They found parasympathetic activity in about one-half the subjects and sympathetic activity in the other half. If autonomic disturbances are definitely established in this disease, another problem arises, i.e., how to account for the normal cholinesterase levels.

#### SUMMARY

The controversy over the presence of cholinesterase in the normal aqueous is discussed.

On purely theoretic grounds, there should be at best only faint traces of cholinesterase in the aqueous, since the enzyme is a protein.

Aqueous from the eyes of 10 normal cats showed either no, or insignificant traces of, cholinesterase.

The first and second aqueous after paracentesis showed marked cholinesterase activity.

The amount of cholinesterase in the aqueous after a paracentesis as compared with cholinesterase values for plasma parallels closely the amount of protein in the aqueous after a paracentesis as compared with plasma protein levels.

# ELECTROPHORETIC PATTERNS OF CONCENTRATED AQUEOUS HUMOR OF RABBIT, CATTLE AND HORSE

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**A**NALYTIC DATA concerning the naturally occurring proteins of the aqueous humor are scant, the measurements presenting two major difficulties: the small amount of available fluid and its low protein content. Duke-Elder<sup>1</sup> separated albumin and globulin in pooled aqueous of three species of animals by fractional precipitation with neutral salts and found the albumin-globulin ratio similar to that occurring in the serum of the respective species. The specific identity of the fractions separated from the horse aqueous with serum albumin and serum globulin of this species was demonstrated by Duke-Elder<sup>1</sup> on the basis of their antigenic properties. Kronfeld<sup>2</sup> obtained in several instances positive precipitin reactions with human aqueous on serums of rabbits which were immunized with human serum albumin and globulin. It was assumed, therefore, that the proteins in the aqueous of normal eyes in the examined species originated mainly in the blood serum, with a possible inconspicuous admixture of proteins arising from other sources (cytolysis, lens proteins).

Attempts to characterize the aqueous proteins by the moving boundary electrophoretic method perfected by Tiselius have not been reported. This method permits the observation in a homogeneous electric field of the mobilities of various components of a protein mixture and of the concentration of each component as measured by the refractive index increment of its boundary. The mobilities depend on the average surface charge per unit area of the molecules, and the direction of migration depends on the sign of this charge. From the electrophoretic pat-

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1. Duke-Elder, W. S.: The Nature of the Intraocular Fluids, *Brit. J. Ophth.*, 1927, supp. 3.

2. Kronfeld, P. C.: The Protein Content of the Aqueous Humor in Man, *Am. J. Ophth.* 24:1121, 1941.

tern, the relative concentration of the individual fractions can be approximately computed by integrating the area under each peak of the pattern. Kabat, Landow and Moore<sup>3</sup> determined the electrophoretic pattern of cerebrospinal fluid of individual patients by concentrating large volumes of the fluid (up to 80 cc.) to about 2 cc. for measurement in a microcell of this capacity. A similar technic was used in the present study.

#### TECHNIC

A total of 40 cc. of aqueous was withdrawn from the eyes of 80 normal rabbits, with the use of local anesthesia induced with dibucaine hydrochloride, 0.1 per cent, with the usual precautions. A total of 5.8 cc. of aqueous was aspirated from 20 rabbits one hour after treating the eyes iontophoretically from the anode with a solution of 0.1 per cent physostigmine salicylate U.S.P. and 0.1 per cent histamine phosphate U.S.P. at 1 milliampere for one and one-half minutes. In 12 eyes severe inflammation was produced by intravitreal injection of 0.1 cc. of staphylococcus toxin, according to the technic described in a previous paper.<sup>4</sup> A total of 2.9 cc. of aqueous was withdrawn when the inflammation appeared at its height. In this series, 6 mg. of sodium citrate per cubic centimeter of fluid was added to prevent coagulation.

Forty-five cubic centimeters of aqueous was collected from the eyes of freshly slaughtered cattle one to three hours after death. Seventy cubic centimeters of aqueous of horses was obtained during the process of bleeding the animals to death.

In all instances the protein content of the original aqueous fluid and that of the concentrated samples were determined nephelometrically according to the method of Looney and Walsh,<sup>5</sup> using the microcuvette designed for the Coleman nephelometer. With the technic used by Kabat, Moore and Landow for cerebrospinal fluid, the aqueous was placed for concentration in a cellophane dialyzing membrane and exposed to nitrogen having a constant pressure of 250 mm. of mercury at refrigerator temperature for several days. The aqueous, concentrated to a volume of about 2 cc., was then redialyzed for twenty-four hours against a buffer 0.02 molar with respect to sodium phosphate and 0.15 molar with respect to sodium chloride ( $p_H$  7.4). The electrophoretic determination of the protein components in the samples of concentrated aqueous was carried out in a microcell having a capacity of 2 cc. The apparatus and method have already been adequately described.<sup>6</sup> The aqueous humors of rabbit, horse and cattle were concentrated 20, 35, and 22.5 times, respectively. Rabbit aqueous from eyes treated with

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3. Kabat, E. A.; Landow, H., and Moore, D. H.: Electrophoretic Patterns of Concentrated Cerebrospinal Fluid, *Proc. Soc. Exper. Biol. & Med.* 49:260, 1942. Kabat, E. A.; Moore, D. H., and Landow, H.: An Electrophoretic Study of the Protein Components, *J. Clin. Investigation* 21:571, 1942.

4. von Sallman, L., and Di Grandi, J.: Controversial Points in Ocular Penicillin Therapy, *Arch. Ophth.*, to be published.

5. Looney, J. M., and Walsh, A. I.: The Determination of Spinal Fluid Protein with the Photoelectric Colorimeter, *J. Biol. Chem.* 127:117, 1939.

6. Tiselius, A.: A New Apparatus for Electrophoretic Analysis of Colloidal Mixtures, *Tr. Faraday Soc.* 33:524, 1937. Longworth, L. G.: Recent Advances in the Study by Electrophoresis, *Chem. Rev.* 39:323, 1942. Ross, V.; Moore, D. H., and Miller, E. G., Jr.: Proteins in Human Seminal Plasma, *J. Biol. Chem.* 144:667, 1942.

histamine and physostigmine was concentrated 2.9 times. The aqueous of the eyes given injections of staphylococcus toxin was used unconcentrated. All the serums were diluted with 3 volumes of phosphate saline buffer at  $p_H$  7.4 before analysis. The concentration of the electrophoretically characterized components in the original aqueous was calculated by multiplying the total protein content of the fluid by the percentage composition of that component as measured in the electrophoretic pattern. The method is subject to a small error, since the specific refractive indexes of all the components may not be identical. With this technic, the mobilities and concentrations of the protein components of normal and pathologic rabbit aqueous and of normal cattle and horse aqueous were determined.

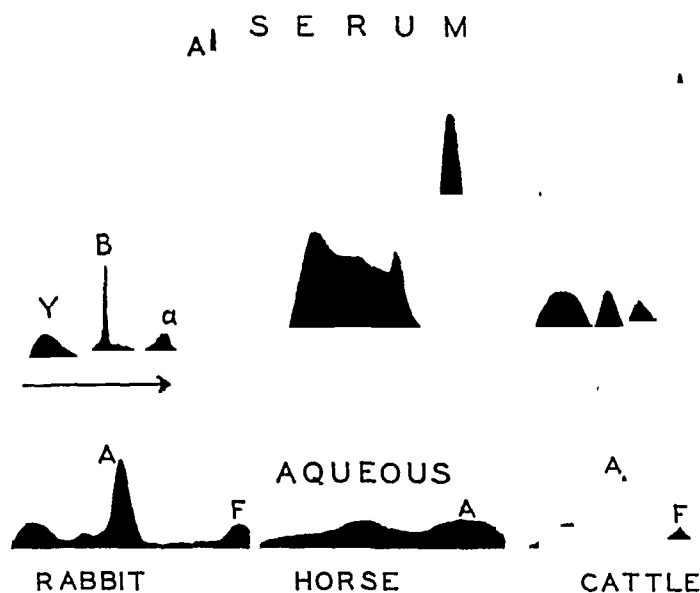


Chart 1.—Comparative electrophoretic pattern of serums and aqueous humors. Before analysis, all the serums were diluted with 3 volumes of phosphate saline buffer at a  $p_H$  of 7.4. The aqueous humor of rabbit, horse and cattle were concentrated 20, 35 and 33.5 times, respectively, by dialysis under pressure.

## RESULTS

The results are presented in the accompanying table. They show, as is illustrated by the patterns (chart 1), that the albumin-globulin ratios for the normal aqueous of the three species of animals were similar to those of the respective serums. The rabbit and horse aqueous contained only two globulins, however, and the globulins of the cattle aqueous were poorly defined. The albumin-globulin ratio for the aqueous of rabbits was 1.4; that for cattle aqueous, 1.1, and that for horse aqueous, 0.74. The ratio was raised to 2.34 for the aqueous of rabbit eyes treated with vasodilators. The normal aqueous of rabbits and that of cattle contained a small amount of a component with a mobility greater than that of albumin; but, because of its small magnitude, identification was not attempted (E in chart 1). The aqueous of rabbit eyes which had been subjected to iontophoretic treatment with vasodilators also did not reveal peaks in the electrophoretic pattern for  $\beta$ -globulin or fibrinogen (chart 2A), whereas these fractions were present in the pattern of the aqueous

*Electrophoretic Fractionation of Serums and Aqueous Humors of Rabbit, Horse and Cattle*

Species	Material	Treatment	Percentage Composition Globulin							Albumin- Globulin Ratio	Globulin Mobilities				
			Fast Compo- nent	Albu- min	$\alpha$ Globulin	$\beta$ Globulin	Fibrin- ogen	$\gamma$ Glob- ulin	Fast Compo- nent		Albu- min	$\alpha$ Globulin	$\beta$ Globulin	Fibrin- ogen	$\gamma$ Glob- ulin
Rabbit	Serum; aque- ous	Normal		56.1	12.7	17.2		14.0	1.27		5.25	3.36	2.79		1.08
			16.4	49.1	7.3			27.2	1.42*	12.2	5.96	3.82			1.18
Horse	Serum; aque- ous	Normal		36.7	12.3	21.6		29.4	0.58		5.30	3.44	2.50		0.96
				42.5		42.5		15.0	0.74		5.06		2.50		0.72
Cattle	Serum; aque- ous	Normal		53.2	9.5	11.7		25.6	1.14		5.20	3.63	2.63		1.25
			9.3	48.2	13.0			29.5	1.13*	9.6	5.50	3.28			1.18
Rabbit	Aque- ous	After ion- tophoresis with hista- mine and physostig- mine		61.5	14.1			24.4	2.34†		5.2	3.3			1.00
Rabbit	Aque- ous	After Injec- tion of sta- phylococcus toxin		63.8	3.8	12.4	8.5	11.5	1.13		4.50	3.40	2.63	1.90	1.25

\*Fast component omitted.

†Fibrinogen omitted.

proteins of rabbits with endophthalmitis induced with staphylococcus toxin (chart 2*B*).

#### COMMENT

The data on serums of rabbits, cattle and horses refer to individual samples of each species but fall into the range of values reported by Moore<sup>7</sup> and by Svensson<sup>8</sup> in extensive investigations of species differences in serum protein patterns. Small quantities of both albumin and globulin were found to occur in the aqueous in about the same ratio as they do in the serum. Two differences, however, appeared: 1.  $\alpha$  and  $\beta$  globulins were either low or absent in the aqueous. 2. The aqueous of normal rabbit and cattle eyes contained a component having a mobility greater than albumin.

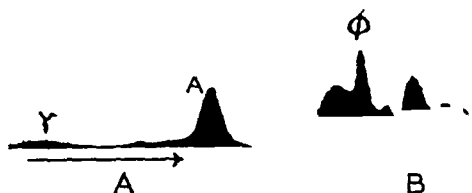


Chart 2.—Rabbit aqueous after eyes had (*A*) been subjected to iontophoretic treatment with solution of physostigmine and histamine or (*B*) staphylococcus toxin had been injected. The aqueous humor of eyes treated with iontophoresis (*A*) was concentrated 2.9 times; that of eyes given injections of toxin (*B*) was not concentrated.

The absence of  $\beta$  globulin may be significant, since the component is partially ether soluble and carries the opalescence of serum.<sup>9</sup> The fast component is possibly hyaluronic acid or a hyaluronic acid-protein complex. The presence of this component in serum, however, was not excluded, since the former was concentrated about twenty times in order to make its appearance in the aqueous, whereas the serums were diluted four times. A similar fast component was also observed in concentrated spinal fluid. There was no reason to assume that the boundary which indicated the small fast component belonged to the false moving boundaries described by Svensson,<sup>10</sup> because the protein content of the samples

7. Moore, D. H.: Species Differences in the Serum Protein Patterns, *J. Biol. Chem.* **161**:21, 1945.

8. Svensson, H.: Electrophoresis by the Moving Boundary Method: A Theoretic and Experimental Study, *Ark. Kemi. min. geol.* **10**:1, 1946.

9. Blix, G.: Electrophoresis of Lipid-Free Blood Serum, *J. Biol. Chem.* **137**:495, 1941.

10. Svensson, H., cited by Blix,<sup>9</sup> p. 161.



was low and the ionic strength of the buffer high. In addition, no false boundaries have been observed in this phosphate buffer mixture.

The resemblance to plasma of the pooled rabbit aqueous in the experiments with staphylococcus toxin suggested that in the acute stage of inflammation all the plasma proteins were drawn into the aqueous. The iontophoretic introduction of the physostigmine and histamine salts gave rise to an increased content of protein in the aqueous (about 300 mg. per cubic centimeter) with an almost twofold increase in the albumin-globulin ratio. It seemed that the transient capillary dilatation rendered the wall of the vessel permeable to the relatively small albumin molecule, whereas the components of greater molecular size were retained by the membranes of the blood-aqueous barrier. Such elevation of the albumin-globulin ratio was observed to an even higher degree by Ayo and Meyer<sup>11</sup> in rabbit aqueous after the intravenous injection of *Escherichia coli* toxin. It is known that a light beam passing through a solution of albumin produces less Tyndall scattering per unit of nitrogen than it does in solutions of the other serum proteins. This optical behavior and the demonstrated shift of the albumin-globulin ratio in the aqueous of moderately irritated eyes may explain some of the discrepancies between the colloidometrically measure intensity of the aqueous flare and the respective protein content of the aqueous of human eyes.<sup>12</sup>

#### SUMMARY

Electrophoretic patterns of pooled aqueous humors from rabbit, horse and cattle were compared with those of the serums of the respective species. Besides the great difference in the total protein concentration of these body fluids, the aqueous exhibited a fast component not apparent in the serum and contained only two globulin components.

In the aqueous of inflamed eyes of rabbits the presence of albumin,  $\alpha$ ,  $\beta$  and  $\gamma$  globulins, and fibrinogen was indicated.

Vasodilation in the anterior segment of the eye induced with histamine and physostigmine resulted in a considerable increase in the albumin: globulin ratio.

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11. Ayo, C., and Meyer, K.: Protein Content of Rabbits' Aqueous Humor Following Intravenous Injection of *E. Coli* Toxin, *Proc. Soc. Exper. Biol. & Med.* **51**:130, 1942.

12. Kronfeld, P. C.: The Limits of Tyndallimetry in the Anterior Chamber, *Am. J. Ophth.* **24**:51, 1941.

# EFFECT OF INTRAMUSCULAR ADMINISTRATION OF MORPHINE, ATROPINE, SCOPOLAMINE AND NEOSTIGMINE ON THE HUMAN EYE

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AND

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A CONSIDERABLE amount of data has been collected concerning the effects of locally administered drugs on the human eye; the indications and contraindications for the use of such drugs are well known to members of the medical profession. On the other hand, information is limited as to the effects on the eye of these same drugs when administered systemically in their usual dosage. Patients with ocular diseases, such as glaucoma, may occasionally be given morphine or atropine for the treatment of a concomitant disease. General surgeons commonly use morphine, atropine, scopolamine and neostigmine in either the pre-operative or the postoperative care of patients, without definite knowledge of the effect of these drugs on incidental diseases of the eye. Morphine is said to increase the intraocular pressure when administered systemically.<sup>1</sup> This action would contraindicate its use in some cases of glaucoma.

Therefore, data were obtained concerning the effect of morphine on size of the pupil, accommodation and intraocular pressure in normal and in glaucomatous eyes. At the same time, information was acquired on the effect of systemically administered atropine, scopolamine and neostigmine on pupillary size and accommodation; it was not possible to measure intraocular tension in these cases.

## METHOD

Twenty-five normal subjects received 8 to 18 mg. of morphine sulfate intramuscularly. Eight patients with glaucoma (3 with chronic simple glaucoma, patients 31, 32 and 33; 2 with glaucoma secondary to uveitis, patients 26 and

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1. Myashita: *Zentralbl. Biochem. Bioph.* 15:95, 1913; cited by Sollmann, T.: *A Manual of Pharmacology*, ed. 6, Philadelphia, W. B. Saunders Company, 1943, p. 277.

TABLE 1.—*Ocular Changes Following Intramuscular Injection of Morphine Sulfate*

Subject No.	Change in Pupillary Size, Mm.		Change in Near Point, Cm.		Change in Tension, Mm.		Dose of Morphine Sulfate, Mg.
	O. D.	O. S.	O. D.	O. S.	O. D.	O. S.	
1	—2.5	—2.5	—3.5	—1.5	—3	—6	8
2	—1.0	—1.0	—2.0	—3.0	0	—1	8
3	—1.5	—1.5	—1.5	—1.5	—7	0	8
4	—1.5	—1.5	—2.5	—1.5	—3	—6	8
5	—3.0	—3.0	—	—	—3	—5	8
6	—1.0	—1.5	—	—	—1	+4.5	8
7	—2.0	—1.0	—	—	0	—2.5	8
8	—1.5	0	—	—	0	—2	8
9	—2.5	—3.0	+0.3	+0.4	—	—	8
10	—2.0	—2.0	—1.5	—2.0	—	—	8
11	—3.0	—3.0	—1.0	—1.5	—	—	8
12	*	*	—	—	—1	—2	8
Average	—1.9		—1.6		—2.2		
13	—3.0	—3.0	—1.8	—1.1	—	—	15
14	—	—	—1.0	—1.0	—	—	15
15	—2.0	—2.0	—1.0	—0.5	—	—	15
16	—2.0	—2.0	—2.5	—4.2	—	—	15
17	—5.0	—5.0	—6.5	—5.2	—	—	15
18	—4.0	—4.0	—3.7	—3.0	—	—	15
19	*	*	—	—	—5	—3	15
20	*	*	—	—	—1	—1	15
21	*	*	—	—	—1	+1	15
22	*	*	—	—	0	+1	15
23	*	*	—	—	—2	—2	15
24	*	*	—	—	—6	—5	15
25	—4.0	—4.0	—2.6	—2.0	—	—	18
Average	—3.3		—2.6		—2.0		
26	0	0	—	—	0	0	15
27	0	—	—	—	0	—	15
28	0	—	—	—	—2	—	15
29	0	0	—	—	0	0	15
30	—0.5	—1.0	—	—	—3	—2	15
31	0	—0.5	—	—	—12	—7	15
32	—1	—0.5	—	—	—10	—6	15
33	0	0	—	—	—5	—2	15
Average	—0.2				—3.5		

\*The pupils were measured in bright light, being already constricted. Patients 31, 32 and 33 had chronic simple glaucoma; patients 26 and 29, glaucoma secondary to uveitis; patients 27 and 28, glaucoma secondary to intraocular growths, and patient 30, congenital glaucoma.

29; 2 with glaucoma secondary to intraocular growths, patients 27 and 28, and 1 with congenital glaucoma, patient 30) were given 15 mg. of morphine sulfate intramuscularly. Eight of the normal subjects received 0.6 mg. of atropine sulfate; 8 others received 0.4 to 0.6 mg. of scopolamine hydrobromide, and 6 others, 1.0 to 1.1 mg. of neostigmine methylsulfate, intramuscularly.

In most subjects, the pupillary size was measured before injection and repeatedly for two hours after injection. On subjects 19 to 24, who received morphine, pupillary measurements were made in a brightly sunlit ward; the pupils were constricted to 2.5 mm. or less before injection of the drug, and consequently the measurements of pupillary size were of no value. On all other patients, measurements were made in a room with constant artificial illumination. Near points of accommodation were measured with a Duane line. The intraocular tension was measured with a Schiötz tonometer before the injection of morphine and at one and two hour intervals afterward; a change of 2 mm. of mercury was considered a significant alteration in tension. The occurrence of ocular and systemic symptoms was noted in all subjects.

## RESULTS

*Morphine Sulfate.*—Of the four drugs given systemically, morphine produced the most significant and consistent ocular effects. Even with 8 mg. ( $1/8$  grain) doses, all subjects showed a decrease in pupillary size (average 1.9 mm.) or a shortening of the near point of accommodation (average 1.6 cm.) (table 1). These changes always began within twenty-five to forty minutes (the time of the first postinjection reading). The injection of 8 mg. of morphine sulfate (subjects 1 to 12) was followed by an increase in intraocular tension in only 1 of 18 eyes; in 13 eyes the tension fell, the average decrease being 2.2 mm.

With the usual dose of 15 to 18 mg. ( $1/4$  grain) (subjects 13 to 25), the pupils of all subjects narrowed (average decrease, 3.3 mm.), and the near points of accommodation shortened (average, 2.6 cm). Intraocular tension rose 1 mm. of mercury (Schiötz) in 2 of the 12 eyes, but the average effect was a decrease of 2.0 mm. of mercury (Schiötz). Maximal effects were noted within one and one-half to two hours.

Fifteen milligrams of morphine sulfate was injected into 8 glaucomatous patients (26 to 33) (with tensions ranging from 28 to 65 mm. of mercury) twenty-four to thirty-six hours after all local ocular therapy had been stopped. The injection of morphine was not followed by any increase in intraocular tension in these eyes. The decreases in tension ranged from 0 to 12 mm. of mercury and averaged  $-3.5$  mm. of mercury. Morphine did not significantly alter the intraocular pressure in any of the glaucomatous eyes except those with chronic simple glaucoma, and possibly 1 eye with congenital glaucoma. Only slight pupillary constriction occurred in the glaucomatous patients.

*Atropine Sulfate.*—Although each subject receiving 0.6 mg. ( $1/100$  grain) of atropine sulfate complained of dryness of the mouth and

throat, only 3 of the 8 subjects had any mydriasis. The range in pupillary change was from 0 to +1.5 mm., the average being +0.4 mm. (table 2). A lengthening of the near point was observed in 10 of the 16 eyes;

TABLE 2.—Ocular Changes Following Intramuscular Injection of Atropine, Scopolamine and Neostigmine

. 0.6 Mg. of Atropine Sulfate				
	Change in Pupil Size		Change in Near Point	
	O. D.	O. S.	O. D.	O. S.
1	+0.5	+0.5	+1.2	-0.7
2	0	0	+2.8	+1.2
3	+1.5	+1.5	+1.7	+1.7
4	+1.0	+1.0	-0.2	+2.2
5	0	0	-0.5	+0.5
6	0	0	-0.9	-0.7
7	0	0	+1.8	+1.4
8	0	0	+0.9	-0.3
Average	+0.4		+0.8	
0.4 to 0.6 Mg. of Scopolamine Hydrobromide				
1	+1	+1	+2.2	+1.5
2	+1.5	+2	+1.8	+4.2
3	+1	+1	-2.1	-0.5
4	0	0	+0.5	-
5	+1	+1.0	+10.0	+6.6
6	+2	+2	+5.7	+4.7
7	+0.5	+0.5	+2.8	+1.3
8	+1	+1	+0.7	+1.5
Average	+1.0		+2.7	
1.0-1.1 Mg. Neostigmine Methylsulfate				
1	+0.5	+0.5	-1.2	-0.8
2	+0.5	+0.5	+0.5	+0.7
3	0	0	-1.6	-3.5
4	0	0	-0.5	+0.5
5	-1	-1	+1.5	+0.9
6	0	+0.5	-	+1.5
Average	+0.2		-0.2	

the range of changes in the near point was -0.7 to +2.8 cm., and the average was +0.8 cm. The maximal effects were noted within one to one and one-half hours.

*Scopolamine Hydrobromide*.—Seven of 8 patients receiving 0.4 to 0.6 mg. (1/150 to 1/100 grain) of scopolamine hydrobromide experienced mydriasis (average increase in pupillary size, 1.0 mm.). Weakening of accommodation occurred in 13 of 15 eyes (average change in near points, 2.7 cm.). Practically all the subjects complained of dryness of the mouth and vertigo, beginning within five to twenty minutes after the injection. One subject complained of blurring of vision and 2 others of ocular discomfort.

*Neostigmine Methylsulfate*.—The ocular effects produced by neostigmine were slight and inconsistent, though all subjects had some systemic symptoms, such as abdominal pain or twitching of skeletal muscles, appearing within an average of thirty-five minutes after the injection. Lacrimation and twitching of the eyelids occurred in 1 subject. The changes in pupillary size and accommodation were all within the limit of error of the methods.

#### COMMENT

The effect of morphine on the pupil is well known; this study merely confirms the observation that decided pupillary constriction follows even small doses (8 mg.) given intramuscularly. The same dose also produced definite increase in accommodative power of the eye. More important than either of these actions is the effect on intraocular tension. Though it is said that morphine produces a rise in intraocular tension, the present studies show that the characteristic effect of morphine is to lower intraocular tension. In glaucomatous patients, the only change produced by morphine was a fall in intraocular pressure. Though morphine is certainly not recommended as a therapeutic agent for any type of chronic glaucoma, it is not contraindicated in glaucomatous patients, since its only action might be a beneficial one so far as the effect on the eye is concerned. This statement, of course, does not apply to its use after ophthalmic operations, when vomiting may be disastrous. The method by which morphine lowers intraocular tension is not known. It may be through its effect on the scleral spur and ciliary muscle. As can be seen from table 1, morphine may lower the intraocular tension without increasing the miosis.

These effects of morphine are not produced by local ocular instillation but occur only after systemic absorption. The effects are said to be due to an action on the oculomotor nuclei in the brain.

It was surprising to find that atropine sulfate (0.6 mg. administered intramuscularly) produced so little effect on the eye. In slightly lower or in the same dosage, scopolamine produced much more consistent and powerful effects on pupillary size and accommodative power. The dose in all cases was sufficient to cause dryness of the mouth and throat. In the

case of patients with glaucoma undergoing surgical procedures (or otherwise requiring the systemic use of atropine or scopolamine), preference should be given to atropine because of its lesser effect on the eye. Even atropine, however, should be used with caution in such patients.

Neostigmine can be administered systemically in ordinary doses to patients with ocular disease without fear that it will produce well defined effects on the eye.

#### CONCLUSIONS

1. Morphine sulfate, in doses ranging from 8 to 18 mg. administered intramuscularly, produced pupillary constriction, increase in accommodative power and decrease in intraocular tension in normal eyes.

2. Morphine produced similar effects in glaucomatous eyes; in none of the 14 eyes in this study did its use lead to an increase in intraocular pressure.

3. In equivalent doses, atropine produced much less pupillary dilation and weakening of accommodation than did scopolamine (both drugs were administered intramuscularly).

4. Neostigmine, in a dosage which produced definite increase in intestinal peristalsis, had no consistent ocular effects.

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## DELAYED KERATITIS DUE TO MUSTARD GAS (DICHLORODIETHYL SULFIDE BURNS)

Report of Two Cases

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**N**O REPORT of delayed keratitis due to mustard gas (dichlorodiethyl-sulfide) burns among United States veterans of World War I appeared in the literature until the recent review of Scholz and Woods.<sup>1</sup> However, many such cases have been reported in the British, French and German literature,<sup>2</sup> so that the condition is a well recognized entity. Goulden<sup>3</sup> stated that 51 men from the British army were blinded and 180 received pensions because of visual disability due to mustard gas in World War I.

There may not have been as many gas casualties in the Army of the United States as there were in the British army. However, a report<sup>4</sup>

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Read at the Eigthy-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 5, 1947.

1. Scholz, R. O., and Woods, A. C.: Relapsing and Chronic Ocular Lesions Following Mustard Gas Burns, *Arch. Ophth.* **37**:137 (Feb.) 1947.

2. Mann, I., and Pullinger, B. D.; *Brit. J. Ophth.* **26**:503, 1942. Mann, I.: *Proc. Roy. Soc. Med.* **35**:236, 1942; *Brit. M. J.* **1**:353, 1942. Neame, H.: *Proc. Roy. Soc. Med.* **22**:25, 1928; *Brit. J. Ophth.* **29**:102, 1945. Heckford, F.: *Proc. Roy. Soc. Med.* **30**:949, 1937. Moore, R. F., and Heckford, F.: *Brit. M. J.* **1**:497, 1929. Whiting, M. H.: *Proc. Roy. Soc. Med.* **33**:225, 1940. de Courcy, T. L.: *Brit. J. Ophth.* **27**:54, 1943. Anglade, M., and Imbert, G. G.: *Ypérite: Le plus redoutable des gaz de combat*, Paris, LeFrancois, 1939, p. 43. Genet, L., and Delord, E.: *Bull. Soc. d'opht. de Paris*, 1936, p. 521; *Lyon méd.* **158**:216, 1936. Genet, L.: *Bull. Soc. d'opht. de Paris* **49**:409, 1937; *Lyon méd.* **160**:229, 1937. Bonnet, P.: *Bull. Soc. d'opht. de Paris* **51**:407, 1939. Parlange, J. A. A.: *Arch. d'opht.* **46**:87, 1929. Péisme, P.: *ibid.* **41**:278, 1924. Sourdille, G. P.: *Bull. Soc. d'opht. de Paris*, 1936, p. 799. Villard, H., and Dejean, C.: *Arch. Soc. d. sc. méd. et biol. de Montpellier* **14**:16, 1933. Weill, G.: *Bull. Soc. d'opht. de Paris* **51**:281, 1939. Worms, G., and Bolotte: *ibid.*, 1926, p. 133. Worms, G.: *Soc. de méd. mil. franç.*, *Bull.*, Paris **20**:229, 1926. Muntsch, O.: *Leitfaden der Pathologie und Therapie der Kampfgaserkrankungen*, Leipzig, Georg Thieme, 1939: Cornea, p. 112. Roesc, H. F.: *Zentralbl. f. d. ges. Ophth.* **28**:513, 1932-1933. Rohrschneider, W.: *Klin. Monatsbl. f. Augenh.* **99**:447, 1937.

3. Goulden, C. B.: *Proc. Roy. Soc. Med.* **33**:235, 1940.

4. Personal communication to the author.



from the Office of the Surgeon General of the United States Army estimates that 52,889 casualties due to mustard gas burns were admitted to hospitals. The corneas of some of these men undoubtedly were seriously affected, as were those in the 2 cases reported in this paper. These cases, however, are typical of those reported abroad, so that they add nothing to knowledge of the lesion.

The purpose of this communication is to review briefly the signs and symptoms of delayed gas keratitis, so that more cases may be recognized and the service connection of the lesions established. Lack of recognition of the condition prevents a veteran so disabled in World War I from receiving the proper consideration, as was true in the 2 cases reported here. Time passed and considerable correspondence took place before the service connection of the disability was established in these cases.

The case reported by McKellar<sup>5</sup> of recurring keratoconjunctivitis which developed ten months after exposure to mustard gas is often referred to. The lesion in this case should probably be considered an exacerbation of the acute stage, rather than the type referred to as delayed keratitis, which develops eight or more years after exposure to the mustard gas.

Mann and Pullinger<sup>6</sup> stated that many of the pathologic changes observed in cases of delayed mustard gas keratitis may be induced by agents other than mustard gas. The diagnosis rests on a combination of the nonspecific lesions with the typical vascular and degenerative changes in a definite time relationship and at a definite anatomic site. They found the lesions due to mustard gas which were produced experimentally in rabbits had a marked similarity to those that occur in the human cornea.

The most characteristic signs given by Mann and Pullinger to identify the keratitis caused by mustard gas are the ulceration of the superficial deposits of cholesterol, the peculiar varicosities and the blood islands. These signs, they stated, have not been induced in rabbits by any other means, or observed in man in conditions other than mustard gas keratitis.

Mustard gas, dichlorodiethyl sulfide, was first employed by the German army in July 1917, after which there were numerous casualties due to the gas. A beautifully illustrated description of the early effects of mustard gas on the eyes was given by Derby<sup>7</sup> at a meeting of this society in 1919.

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5. McKellar, J. H.: *Am. J. Ophth.* 3:309, 1920.

6. Mann, I., and Pullinger, B. D.: *Am. J. Ophth.* 26:1253, 1943.

7. Derby, G. S.: *Tr. Am. Ophth. Soc.* 17:90, 1919; *Am. J. Ophth.* 49:119, 1920.

The course is similar in all cases. After exposure to mustard gas, the action is delayed from two to six hours. The early symptom is irritation of the eyes, nose and throat, with sneezing and sometimes vomiting. The inflammation of the mucous membrane and skin increases, and may be followed by blistering. Symptoms referable to the respiratory tract increase, with severe bronchitis, and secondary pneumonitis frequently develops. The severity of the ocular and general symptoms depends on the amount of exposure and the susceptibility of the individual patient.

Whiting<sup>8</sup> classified persons affected with mustard gas as follows: All had photophobia and blepharospasm. Class 1, comprising about 75 per cent, had comparatively mild symptoms without corneal involvement. In class 2, totaling about 15 per cent, the eyes were moderately affected; the corneas were a little roughened but did not stain. In class 3, fortunately only about 10 per cent, the eyes were severely affected, both the cornea and the conjunctiva being involved. The area of the palpebral fissure was severely burned and presented solid white edema of the conjunctiva. The epithelium of the exposed cornea, involving the lower one half or two thirds, was gray and stained with fluorescein. It is from this 10 per cent in class 3 that "delayed keratitis" developed eight or more years later. If the eyes of 10 per cent of the 50,000 mustard gas casualties admitted to hospitals of the Army of the United States were similarly affected, several thousand United States veterans might be expected to have delayed mustard gas keratitis with defective vision.

Lister<sup>9</sup> reported the following early pathologic changes which were observed in eyes burned with mustard gas. The corneal epithelium was denuded, with flattening of the remaining cells. The white appearance of the conjunctiva noted in the early stages of the severer burns was due to coagulation and arrest of circulation in the conjunctival vessels. The substantia propria showed round cell infiltration in some cases. Later, the appearance was reversed; the exposed area was injected, and the vessels remained permanently enlarged, while the rest of the conjunctiva appeared normal.

Phillips,<sup>10</sup> who collected 70 cases, called attention to the similarity of the histories of persons with delayed keratitis due to mustard gas. They were unable to open their eyes for about a week owing to the severe photophobia and blepharospasm, which was accompanied with profuse lacrimation. After being confined to the hospital four to six months or longer, they were comparatively free from symptoms for ten to fourteen

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8. Whiting, M. H.: *Proc. Roy. Soc. Med.* 33:225, 1940.

9. Lister, W., in Macpherson, W. G.: *History of the Great War Based on Official Documents: Medical Services, Surgery of the War*, London, His Majesty's Stationery Office, 1922, vol. 1.

10. Phillips, T. J.: *Proc. Roy. Soc. Med.* 33:229, 1940.

years. The onset of the delayed keratitis was marked by one or all of the following symptoms: photophobia, lacrimation and failing vision. The lower third of the cornea was affected most. Superficial ulceration occurred, and the sensibility of the cornea was less than normal. Phillips described gray, branching lines in the substantia propria seen with the slit lamp; these he compared to "skate marks on fresh ice." The pale, triangular patches on either side of the cornea he spoke of as "marbling." In these patches there was absence of small conjunctival and episcleral vessels, leaving large areas of the sclera bare, and here and there was a large distended vessel, which was more tortuous as it neared the limbus and ended in a small, corkscrew-like vessel.

This brief clinical account of the condition corresponds closely with the lesions produced experimentally with mustard gas in rabbits by Mann and Pullinger,<sup>6</sup> who stated that "late keratitis" is a slow degenerative process, seen in man up to twenty years after exposure to mustard gas.

#### REPORT OF CASES

CASE 1.—D. O., aged 47 years, when seen in February 1939, had the signs and symptoms of "delayed mustard gas keratitis" well established. I had examined him in 1917, prior to his entrance into the service, and at that time his eyes were normal, with vision of 20/15 in each eye. On Oct. 4, 1918, while asleep in a cellar, a gas shell burst near him. Although he felt all right, he reported to the first-aid station, where he slept the rest of the night. On awakening in the morning, he was nauseated and found it difficult to open his eyes because of photophobia. He was hospitalized for eight months. His lungs were also affected. In 1919 I again examined him, when he said that his eyes were irritated and sensitive to light at times. Except for slight hypermetropic astigmatism, his eyes appeared normal. In 1928 a faint corneal opacity was first observed down and temporally in the left eye, and there was a faint, almost imperceptible, haze of both corneas. Photophobia had increased, but vision was still 20/15 in each eye. In February 1939 failing vision and photophobia were more pronounced, so that he wore an eye shade at his work and avoided bright light. Corrected vision was 20/25 in the right eye and 20/20 in the left eye. There was now a definite, faint, superficial haze involving the lower two thirds of each cornea, being denser in the right eye than in the left. Although the cornea was sensitive to light, the sensibility was less than normal. In October 1939, twenty-one years after he had been gassed, his symptoms had increased in severity, and his corrected vision was reduced to 20/40 in the right eye and 20/25—2 in the left eye. The corneal haze was denser in each eye, and there were striae in the substantia propria of the right eye and vertical folds in Descemet's membrane. Pale, triangular areas on either side of each cornea were now more apparent. In each eye, the triangle on the right side of the cornea was larger than that on the left. A few tortuous vessels were seen in these areas, and there were a few scattered deposits of cholesterol. The epithelium first began to break down a year later, in July 1940. The right eye was affected first, and the cornea stained in several places. There were many recurrences of the process in the right eye, with progressive degenerative changes. A heaping up of yellowish crusts of degenerated tissue on the cornea caused considerable irritation, and the lesions were removed. The vessels in the

triangles, particularly the temporal one in the right eye, became larger and more tortuous, and vision in the right eye was reduced to 20/100. On March 12, 1943, photographs (figs. 1 and 2) showed the degenerative changes to be more advanced in both eyes, and corrected vision was 6/200 in the right eye and 20/25 in the



Fig. 1 (case 1).—Right eye, showing degenerative changes in the cornea, with deposits of cholesterol and tortuous vessels in the pale, atrophic, triangular areas on either side of the cornea.

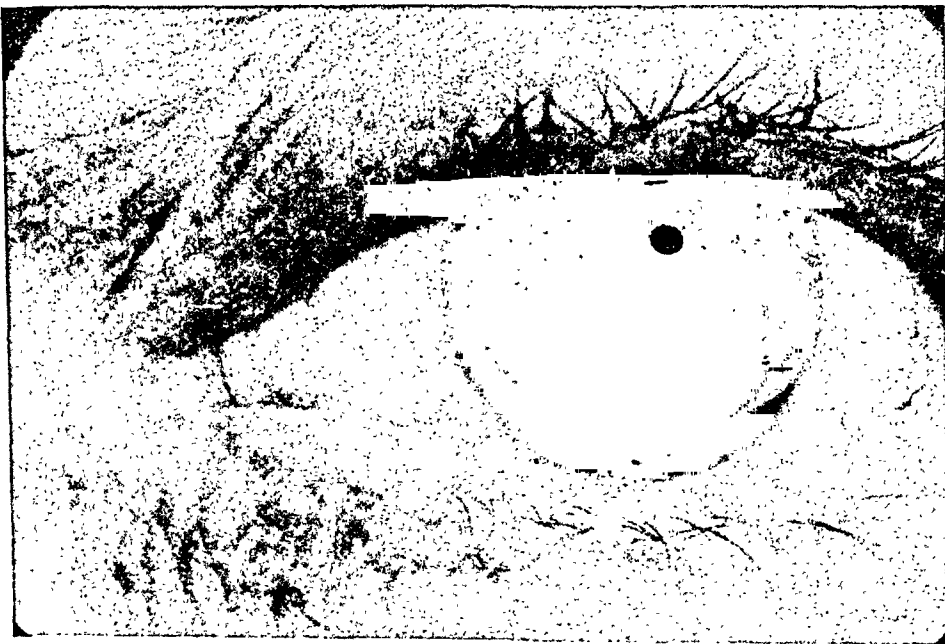


Fig. 2 (case 1).—Left eye, showing a condition similar to that in the right eye.

left eye. On Feb. 26, 1944, the vessel in the temporal triangle of the right eye was larger and more tortuous as it approached the corneal margin. Adjacent to it, in the superficial layers of the substantia propria of the cornea, was an intracorneal hemorrhage. In March 1946, corrected vision was reduced to 3/200 in

the right eye (fig. 3) and to 20/60 in the left eye. The photophobia and lachrymation were increased, but the epithelium was intact. Folds in Descemet's membrane appeared in the cornea of the left eye, and there were a few striae in the substantia propria, similar to those in the cornea of the right eye (figs. 4 and 5).



Fig. 3 (case 1).—Right eye, showing a condition more advanced than that presented in figure 2.

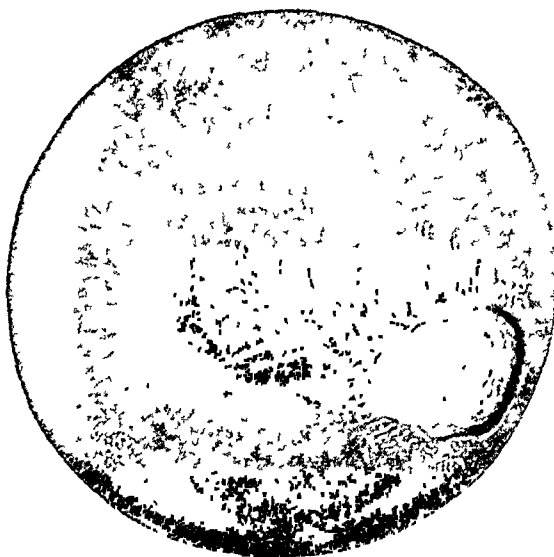


Fig. 4 (case 1).—Left eye, showing folds in Descemet's membrane and a few striae in the substantia propria as seen with the slit lamp.

In February 1947, there was less photophobia, and vision had improved a little in the right eye, to 20/200. This acuity was not improved with glasses. The left eye remained the same, vision being 20/60 with correction. The improvement in

vision was thought to be due to a few clear spots, where the crusts had been removed. Contact lenses were advised.

CASE 2.—R. M., aged 42, was first examined by me on May 21, 1938, twenty years after he had been exposed to a gas shell barrage. The shelling began about 11 p.m., on June 14, 1918, and he had had his mask on and off during the night. In the morning his eyes began to smart and tear and were tightly closed by the time he reached the first-aid station. He was in the hospital for about two months, and his eyes were bandaged for about a month. His lungs were also affected. After discharge from the Army, he had no ocular symptoms until a few months before he consulted me, when he noticed that the vision in his left



Fig. 5 (case 1).—Slit lamp beam, showing depressed area and folds in Descemet's membrane in the left eye.

eye was blurred and that there was a spot on this eye, similar to the spots which later appeared in the cornea of the right eye, and which are shown in figure 6. Vision was 20/15—2 in the right eye and 20/15—4 in the left eye. Both corneas were hazy in the area of the palpebral fissures. The haze, which somewhat resembled a lacy web, appeared to be located just under the epithelium. It was interspersed with small, irregular, white deposits, tinged yellow, with branchlike projections. Some appeared to have coalesced. The condition was more pronounced in the left eye. In each eye, pale, triangular areas were present on each side of the cornea, and in these areas were scattered a few similar yellow deposits and a few tortuous, irregularly shaped vessels. The condition progressed slowly; the deposits became larger, and more of them in the left eye coalesced to form a large, yellowish, irregular elevation (figs. 7 and 8). The sensitivity of the left

cornea was less than that of the right, but both were less sensitive than normal. The elevated patch was removed from the left cornea but many deposits were left. The patient was comfortable until the summer of 1945, when a similar elevation, which caused considerable irritation, developed on the same cornea.



Fig. 6 (case 2).—Cornea of the right eye; early manifestations, consisting in small deposits of cholesterol in the cornea and tortuous vessels.



Fig. 7 (case 2).—Cornea of the left eye, showing a more advanced stage, with coalescence of yellow deposits and tortuous vessels.

The right cornea was a little hazier, with vision of 20/20, and in the left eye vision was reduced to 20/200. A keratectomy was done, the thin strip of cornea which contained most of the cholesterol deposits being removed. One month

after the operation his vision was 20/200, being the same as before the operation. On examination in March 1946, he stated that both eyes had been comfortable since the last examination; vision in the right eye was still 20/20, but vision in the

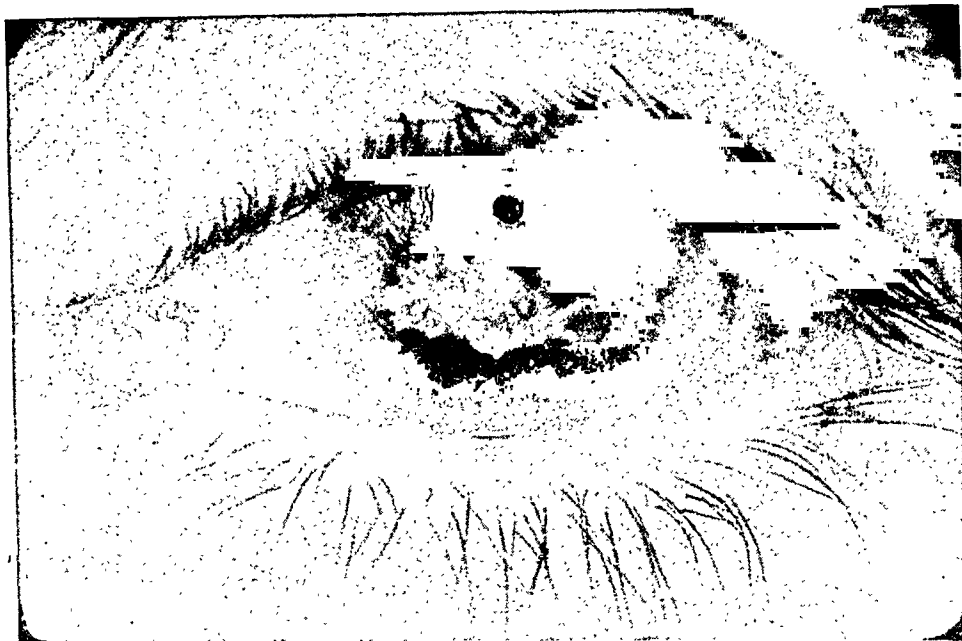


Fig. 8. (case 2).—Cornea of the left eye, showing further coalescence, which formed an irregular elevation of the deposits.



Fig. 9 (case 2).—Left eye, with clear horizontal band corresponding to the site of keratectomy.

left eye was reduced to 8/200, and was not improved with glasses. Both eyes were quiet, and the left eye showed a moderately clear horizontal band corresponding to the site of the keratectomy (fig. 9).



## COMMENT

Late corneal lesions develop more frequently in cases with greater exposure to mustard gas and in those of greater susceptibility to it. The condition is aggravated if the eyes are bandaged during the acute stage following exposure to the mustard gas. Derby<sup>7</sup> mentioned a case in which both eyes were seriously affected by bandaging. Duke-Elder<sup>11</sup> warned against the use of bandages in the acute stage after exposure to the gas and suggested bland symptomatic treatment. It is generally conceded that active treatment in the acute stage is contradicted.

After recovery from acute symptoms, which in cases of severe burns last from two to eight months, and sometimes longer, the patient is practically free from symptoms for eight years or more.

Photophobia, lacrimation and failing vision mark the onset of the late corneal lesions. Superficial haze of the cornea just beneath the epithelium in the area of the palpebral fissure, lines or striae in the substantia propria (figs. 4 and 5) and folds in Descemet's membrane may precede the formation of deposits of cholesterol and fat. These deposits increase in size and break through the epithelium, producing an exacerbation of the symptoms of irritation. Later, there is a heaping up of hard, degenerative tissue on the cornea. As these lesions increase in size, they cause more and more irritation, until they are cast off or removed, leaving rather clear, irregular, depressed spots. The scarred cornea is so irregular that vision is improved very little with glasses. However, with contact lenses an astonishing improvement was reported by Mann.<sup>6</sup> In a case in which there was no improvement with glasses, vision was improved from 6/36 to 6/6 with contact lenses. In a later report, Mann<sup>12</sup> reviewed 84 cases of delayed gas keratitis in which the patients were fitted with contact lenses. In addition to producing great improvement in vision, acuity in 1 case being increased from counting fingers to 6/12, the lenses are tolerated well, owing to decreased sensibility of the cornea. They also afford some protection against minor injuries, and the recurrence of ulceration is less frequent. Nevertheless, a letter<sup>13</sup> from the regional office of the United States Veterans Administration states that contact lenses are issued only to veterans who are unable to wear ordinary frames because of wounds or scars which affect the temples or nose, and that it is unable to approve the issuance of contact lenses for veterans whose vision has been reduced by delayed mustard gas keratitis.

No reports of successful corneal transplants for this condition have been found in the literature.

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11. Duke-Elder, W. S.: *Textbook of Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1714.

12. Mann, I.: *Brit. J. Ophth.* 28:441, 1944.

13. Personal communication to the author.

Other important diagnostic signs are pale, triangular, atrophic-looking patches on either side of the cornea in the area of the palpebral fissures. In the triangles there is absence of conjunctival and episcleral vessels, with an occasional vessel distended, of tortuous, varicose type. There are also a few scattered deposits of cholesterol. These areas have somewhat the appearance of lesions produced by surface application of beta radiation. Intracorneal hemorrhages occur and appear to arise from the large varicose vessels, which extend up to the limbus.

#### CONCLUSION

Recognition of the late effects of mustard gas on the cornea is important in order to establish the service connection of the disability, so that claims of veterans, so disabled in World War I, may be justly handled

Dr. James E. McAskill made the photographs in these cases.

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# TREATMENT OF OCULAR SYPHILIS WITH PENICILLIN

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Although penicillin has been extensively employed in the treatment of various syphilitic infections, only a few reports have been made evaluating its use in ocular syphilis.<sup>1</sup> During the past three years we have used penicillin in the treatment of 39 patients with various manifestations of syphilis of the eye. The results are presented in this report.

## INTERSTITIAL KERATITIS

The efficacy of any form of therapy for interstitial keratitis must be considered in the light of the natural course of this infection. Untreated syphilitic interstitial keratitis involves both eyes in the majority of cases.<sup>2</sup> Involvement of the second eye may occur from weeks to years after that of the first and may lead to functional blindness (vision less than 20/200). The usefulness of one eye is lost in almost 20 per cent of untreated patients and that of both eyes in 6 per cent.<sup>2a</sup> According to Klauder and Van Doren,<sup>3</sup> 35 per cent of untreated patients with interstitial keratitis retain good to excellent vision (20/70 to 20/20) in the poorer eye. Other reports show that 28 to 40 per cent of untreated

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From the Departments of Ophthalmology and Medicine of Grady Hospital and Emory University School of Medicine, and the Georgia Department of Public Health.

1. (a) Klauder, J. V., and Dublin, G. J.: Syphilitic Uveitis: Diagnosis, Herxheimer Reaction and Results of Various Treatments, Including Penicillin Therapy, *Arch. Ophth.* **35**:384 (April) 1946. (b) Moore, J. E.: *Penicillin in Syphilis*, Springfield, Ill., Charles C Thomas, Publisher, 1946. (c) Stokes, J. H.; Steiger, H. P., and others: *Penicillin Alone in Neurosyphilis*, *J.A.M.A.* **131**:1 (May 4) 1946.

2. (a) Moore, J. E.: *The Modern Treatment of Syphilis*, Springfield, Ill., Charles C Thomas, Publisher, 1943. (b) Woods, A. C.: *Syphilis of the Eye*, *Am. J. Syph., Gonorr. & Ven. Dis.* **27**:133, 1943.

3. Klauder, J. V., and Van Doren, E.: *Interstitial Keratitis: Analysis of Five Hundred and Thirty-Two Cases, with Particular Reference to the Standardization of Treatment*, *Ven. Dis. Inform.* **22**:307, 1941; *Arch. Ophth.* **26**:408 (Sept.) 1941.

patients have a final visual acuity of 20/30 or better.<sup>4</sup> Any form of treatment must, of course, show results superior to these before it can be considered of value.

*Case Material and Procedures.*—In this study 15 patients were treated for acute active interstitial keratitis. Three of these patients had had previous episodes of keratitis. The remaining 12 had interstitial keratitis for the first time. Four of these 12 patients were treated on two different occasions for keratitis of first one eye and then the other. The keratitis was considered to be severe or moderately severe in all but 1 of the 15 patients. Thirteen of the patients were Negroes; 2 were white persons. Eleven were female and 4 male. All the patients were thought to have congenital syphilis; none of them had other clinical evidence of an active infection. Quantitative Kahn titers before treatment ranged from 40 to 640 units. Examination of the spinal fluid revealed no evidence of syphilis in any case.

The ages of our patients varied from 6 to 26 years. Eight of the patients were 15 years of age or less. One patient had received previous treatment for syphilis with 2,400,000 units of penicillin six months before the development of interstitial keratitis, while 2 other patients had received a total of ten and thirty injections, respectively, of arsenical and bismuth preparations several years previously. The 3 patients treated for recurrence of their keratitis had received inadequate arsenical and bismuth therapy for their initial keratitis.

In this study, treatment of the keratitis in 5 of the 7 adults consisted of 4,000,000 units of commercial penicillin given in doses of 50,000 units intramuscularly every three hours for ten days. One patient received a total of 2,000,000 units, and another a total of 3,000,000 units. Early in this study the children were given a total dose of 50,000 units of penicillin per kilogram of body weight. This dose was subsequently increased to 100,000 units per kilogram of body weight. Six of the patients who showed no response to penicillin at the completion of treatment were given fever therapy with typhoid vaccine. Three of these 6 patients had recurrent interstitial keratitis. Three patients treated early in this study also received approximately fifteen injections of oxophenarsine hydrochloride U.S.P. and ten injections of a bismuth preparation immediately after penicillin therapy.

Local treatment was given each patient and consisted in complete and prolonged atropinization, use of hot compresses and, in some instances, local instillation of penicillin solution into the eye. The last measure did not appear to increase the effectiveness of the treatment and was used in only a few cases. Local treatment was continued until all the ciliary injection or photophobia was relieved. This often occurred several weeks after penicillin had been completed. After discharge from the hospital, patients were instructed to return every two weeks until the active process had subsided, and then every three or six months. All the patients were observed for at least eight months; 3, from one to two years, and 3, for more than two years.

*Results.*—A total of 20 eyes were treated for the initial infection and 4 eyes for recurrent infection. The final visual acuity for the group with the initial infection eight months to two years after treatment is shown in table 1.

It should be noted that 16, or 80 per cent, of the 20 eyes treated for initial involvement finally showed good to excellent vision. The effect

4. (a) Carvill, M., and Derby, G. A.: *Interstitial Keratitis*, Boston M. & S. J. 193:403, 1925. (b) Dennie, C. C., and Pakula, S. F.: *Congenital Syphilis*, Philadelphia, Lea & Febiger, 1940. (c) Cole, H. N., and others: *Late Prenatal Syphilis, with Special Reference to Interstitial Keratitis: Its Prevention and Treatment*, Arch. Dermat. & Syph. 35:563 (April) 1937. Ven. Dis. Inform. 18:97 1937.

of penicillin treatment, however, was rarely apparent during the period of treatment. Almost all the patients showed as much or more inflammatory reaction at the completion of the ten day treatment as at the beginning. Only 1 patient showed marked improvement during penicillin therapy, and the keratitis recurred in the other eye two weeks later. In 7 of the patients the vision was so impaired at the completion of penicillin treatment that they could not count fingers at a distance greater than 2 feet (60 cm.). Without further treatment the keratitis cleared satisfactorily in three to five months, and 5 of these 7 patients obtained good to excellent vision. The appearance of the eye at the completion of penicillin treatment apparently does not indicate the amount of corneal clearing that may finally result.

TABLE 1.—*Vision Obtained After Treatment in Cases of Initial Infection*

	No. of Patients Treated	No. of Eyes Treated	Excellent 20/20-20/30	Number of Eyes Obtaining Specified Visual Acuity		
				Good 20/40-20/70	Poor 20/100-20/200	Bad 20/200
Penicillin alone	9	16	7	8	1	0
Penicillin and fever	3	4	1	0	2	1
Total	12	20	8 (40%)	8 (40%)	3 (15%)	1 (5%)

Although early in this study fever therapy was given to those patients who failed to respond to penicillin, this additional treatment may not be necessary, since we have found that some of the most severely involved eyes will clear after the use of penicillin alone if observed for a sufficient period.

Of the 4 eyes treated for recurrent interstitial keratitis, 3 had a final visual acuity of 20/200 or less. The remaining eye had 20/100 vision. As was to be expected, the results in these eyes were worse than in those treated for the initial lesion.

*Comment.*—In this series of 15 patients with interstitial keratitis treated with penicillin either alone or combined with artificial fever, not less than 14 obtained good to excellent vision in one or both eyes. Only 1 patient continued to have poor vision in both eyes, and this patient was treated for recurrent keratitis. In general, our results are similar to those obtained by Klauder and his associates,<sup>5</sup> who used penicillin in 55 cases gathered from various clinics. Only 16 of their patients were treated with penicillin alone; the others apparently had a severer infection and received fever therapy in addition to penicillin. Seventy-one per cent of the patients in their study obtained good (20/50 or better) vision.

Penicillin therapy may not prevent involvement of the second eye. Although none of our patients has thus far had recurrence of keratitis in the same eye after penicillin therapy, 1 of them had been given penicillin for latent syphilis six months before her keratitis developed. In another patient, not included in the present series, but previously re-

5. Klauder, J. V., cited by Moore.<sup>1b</sup>

ported on,<sup>6</sup> keratitis developed two weeks after the administration of penicillin for Clutton's arthritis.

These observations, together with the fact that penicillin produced little or no immediate effect on the keratitis, suggests that the course of this condition may not be altered by penicillin therapy. It is obvious that a much larger series of patients should be treated with penicillin before the usefulness of this drug can be accurately evaluated.

Despite these reservations, the results obtained with this small series of patients appear to be better than those obtained with older methods of therapy. The use of routine arsenical and bismuth preparations has been shown to give "satisfactory" results in only 65 per cent of a large series of cases,<sup>7</sup> whereas the addition of fever therapy resulted in good to excellent vision in approximately 55 per cent.<sup>8</sup> The use of penicillin for this condition has certain additional advantages in that it not only acts on the underlying systemic infection but is also non-toxic and does not require a prolonged course of treatment.

The results presented here are better than those which were reported in a preliminary paper on some of this same group of patients.<sup>6</sup> This improvement is due to the fact that considerable restoration of vision comes with longer periods of observation.

Interstitial keratitis remains a difficult disease to treat satisfactorily. Woods and Chesney<sup>9</sup> attributed this refractoriness to treatment to the low concentration of the drug obtained in the avascular cornea. They stated that when penicillin is brought to the cornea in high concentration by iontophoresis rapid healing of the lesion takes place without vascularization. We have not had any experience with this form of therapy.

#### IRITIS

Inflammation of the iris occurs predominantly in the secondary stage of syphilis and usually responds satisfactorily to antisyphilitic and local treatment.

We have treated with penicillin alone 6 patients with secondary syphilis and iritis. The dosage varied from 2,400,000 to 4,000,000 units, given in equally divided amounts intramuscularly every three hours for seven to ten days. Atropine was used locally in addition to intramuscular injection of penicillin. No attempt was made to prevent a Herx-

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6. Yampolsky, J., and Heyman, A.: Penicillin in the Treatment of Syphilis in Children, *J.A.M.A.* **132**:368 (Oct. 19) 1946.

7. Moore.<sup>2a</sup> Klauder and Van Doren.<sup>3</sup> Cole and others.<sup>4c</sup>

8. Carvill and Derby.<sup>4a</sup> Dennie and Pakula.<sup>4b</sup>

9. Woods, A. C., and Chesney, A. M.: Relation of the Eye to Immunity in Syphilis, with Special Reference to the Pathogenesis of Interstitial Keratitis, *Am. J. Ophth.* **29**:389, 1946.

heimer reaction, and none was observed by gross examination in any patient. Three of these patients had unilateral iritis and 3, bilateral. Two had the nodular type. All 6 patients improved rapidly and obtained a final visual acuity of 20/20 in each eye; there were no complications. All these patients also showed striking improvement in their cutaneous manifestations of secondary syphilis and their serologic tests for syphilis have thus far given satisfactory responses.

Klauder and Dublin also obtained good results with the penicillin treatment of this type of iritis.<sup>10</sup> They treated 24 patients, the total dose being 2,400,000 units of penicillin. A Herxheimer reaction was observed either grossly or with the slit lamp in every one of their patients. The results were excellent, and normal vision was obtained in all but 1, a patient who had complete bilateral pupillary occlusion and secondary glaucoma in one eye before treatment.

In addition, we have treated with penicillin 3 patients who had iritis associated with late syphilis. One of these patients had seclusion of the pupil with complicated cataract; the second had a blind eye from previously untreated iritis, and the third had secondary glaucoma. Only the first of these 3 patients appeared to respond to treatment. No significant changes were noted in the other 2 patients.

It is often impossible to determine whether the iritis which occurs in patients with late syphilis is of syphilitic origin. The iritis in our patients may not have been related to their syphilitic infection, and the fact that 2 of them failed to respond to penicillin does not necessarily indicate that the drug is ineffective in treatment of iritis caused by late syphilis.

#### CHOKED DISK

Swelling of the optic nerve is often associated with acute syphilitic meningitis.<sup>2b</sup> This condition may simulate optic neuritis but differs in that there is relatively little impairment of vision. The swelling is probably due to increased intracranial pressure and hyperemia of the disk. Such a condition usually responds satisfactorily to arsenical and bismuth therapy.

We have treated 3 patients with acute syphilitic meningitis who had bilateral papilledema of 1 to 4 D. No disturbance of vision or constriction of visual fields was noted in 2 of these patients. The third patient had slight visual impairment and constriction of the visual fields. This patient had prominent papilledema and was thought at first to have a cerebral tumor. All 3 patients received 4,000,000 units of sodium penicillin intramuscularly, in equally divided doses every three hours for ten days. All showed satisfactory subsidence of the papilledema and relief of the meningeal symptoms. No Herxheimer reaction was noted.

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10. Klauder and Dublin.<sup>1a</sup> Klauder.<sup>5</sup>

The patient who had impaired vision before treatment obtained normal vision shortly after treatment was completed. The spinal fluid and serologic tests have likewise responded satisfactorily to penicillin therapy.

#### PRIMARY ATROPHY OF THE OPTIC NERVE

In the treatment of syphilitic primary atrophy of the optic nerve, arrest of the process is generally considered a satisfactory result. Little or no improvement in visual acuity or the visual fields can be expected after treatment of this condition, since the lesion is usually degenerative and irreversible changes in the optic nerve fibers have usually occurred before treatment is begun. When untreated, 70 per cent of patients with primary optic nerve atrophy are blind in three years, 90 per cent in five years and almost all within seven to nine years.<sup>2b</sup> Several factors are known to influence the prognosis of this condition. In general, patients with unilateral involvement, or patients with bilateral involvement who have good vision in one or both eyes, have a favorable prognosis. The outcome is bad, however, when the vision in the better eye is 20/60 or less.<sup>2a</sup> It should also be borne in mind that many cases of atrophy of the optic nerve have become stationary before treatment is begun and that the efficacy of a new method of treatment can be evaluated only in those cases in which the process is known to be progressive. Moreover, an observation period of at least three years is essential before definite conclusions can be drawn as to the success of treatment.

*Case Material and Procedures.*—There were 12 patients in this study with progressively decreasing vision caused by syphilitic primary atrophy of the optic nerve. In all these patients the spinal fluid showed strongly positive evidence of syphilis, with increased cells and protein, in addition to a positive Wassermann reaction. Eight had received previous treatment for syphilis, consisting usually of inadequate amounts of heavy metals many years before the development of their optic nerve atrophy. One patient (case 8) had received fifty-four hours of fever therapy at temperatures greater than 103F. with typhoid vaccine one year prior to the present admission, but had continued to show progression of the optic nerve atrophy and changes in the spinal fluid. Another patient (case 5) had received 1,200,000 units of penicillin two years previously for what was thought at that time to be asymptomatic neurosyphilis with amblyopia caused by trypanamide. This patient, likewise, had pronounced diminution of vision several months prior to the present admission. All the patients showed definite pallor of the optic disk, decreased visual acuity and constriction of the fields in one or both eyes. Penicillin was given intramuscularly in doses of approximately 50,000 units every three hours for seven to sixteen days, for total doses of 2,400,000 to 6,000,000 units. Four of the patients received fever therapy in addition to penicillin, while the remaining 8 patients received penicillin alone. No other antisyphilitic treatment was employed, and the patients were instructed to return every three months for follow-up observation.

*Results.*—The results obtained with these patients are summarized in table 2. It will be observed that 6 of the 12 patients showed progres-



sion of their optic nerve atrophy six months to two years after treatment. Of the 8 patients treated with penicillin alone, 4 showed apparent arrest of the process. Three of these 4 patients (cases 1, 2 and 9) had moderately severe and recently progressive atrophy of the optic nerve prior to treatment. The other patient (case 3) had had symptoms for four years and might have had a spontaneous arrest, since Moore<sup>2a</sup> has shown that patients not blind at the end of three years usually do well even in the absence of treatment. The period of observation following treatment for these patients is relatively short, and further progression may ultimately occur.

In 6 of our patients the condition progressed to practical blindness. All had had useful vision in one eye before treatment: One of these patients (case 7) received only 2,400,000 units of penicillin, an amount now considered inadequate. This patient had severe hypertension and aortic insufficiency, and fever therapy was contraindicated. This patient has been retreated in another clinic and received 6,000,000 units of penicillin in beeswax together with eight injections of oxyphenarsine hydrochloride and five injections of a bismuth preparation. Examination two years later revealed no further loss of vision. In 2 other patients the atrophy progressed despite penicillin and malarial fever therapy.

No Herxheimer reactions were encountered in these 12 patients, even though large doses of penicillin were given to most of them throughout the entire course of therapy. In 1 patient, not included in this series, however, a severe Herxheimer reaction apparently developed, and he became completely blind after penicillin and malarial therapy.

Regardless of the response of the vision, all the patients showed a satisfactory or improved condition of the spinal fluid six months to a year after penicillin treatment.

*Comment.*—The results obtained in this series with the use of penicillin in the treatment of optic nerve atrophy are comparable to those obtained by other authors. Klauder<sup>5</sup> treated 20 patients with progressive atrophy of the optic nerve with penicillin alone in doses of 4,200,000 units. The condition of 10 of these patients remained stationary throughout observation periods of one to twenty-one months, while that of the remaining 10 patients continued to progress. Six of the latter patients had less than 20/200 vision at the onset of therapy, and deterioration would probably have progressed with any form of treatment. Stokes and his associates<sup>1c</sup> reported the results obtained with penicillin alone in 9 patients with presumably progressive atrophy of the optic nerve. One of their patients became blind; 4 showed further contraction of the visual fields, and 4 showed no change. Improvement in the spinal fluid was noted in almost all their patients despite progression of the ocular process. Another group of 15 patients with atrophy of

TABLE 2.—Summary of Data on 12 Patients with Atrophy of the Optic Nerve Treated with Penicillin

Patient No.	Age	Race	Sex	Duration of Visual Impairment, in Months	Visual Acuity Before Treatment		Dose of Penicillin, Units	Additional Treatment	Months Observed After Treatment	Visual Acuity After Treatment		Final Status
					Right	Left				Right	Left	
1	42	N	F	8	Light	20/70	5,800,000	None	25	Light	20/70	Stationary
2	42	N	M	8	perception	20/50	6,000,000	None	24	8/200	15/70	Stationary
3	47	N	M	48	20/30	Light	5,400,000	None	25	20/30	perception	Stationary
4	35	N	M	1	20/25	Perception	4,000,000	Typhoid Vaccine	23	20/25	20/25	Stationary
5	44	W	F	24	20/20	Blind	6,000,000	Malaria	18	20/20	Blind	Stationary
6	40	N	M	8	Light	20/70	4,800,000	Malaria	21	Light	Finger perception	Progressed
7	58	N	M	6	perception	20/100	2,400,000	None	41	Light	5/200	Progressed
8	38	N	F	24	10/200	20/200	5,300,000	None	23	perception	Light	Progressed
9	63	N	M	12	20/100	20/200	4,800,000	None	11	20/100	perception	Stationary
10	36	N	M	12	20/70	20/100	6,000,000	None	19	20/100	20/100	Progressed
11	31	N	F	3	20/100	1/200	4,800,000	Malaria	13	Light	Blind	Stationary
12	55	N	F	12	20/50	Light perception	4,800,000	None	11	8/200	Light perception	Stationary

the optic nerve were treated by Curtis and his co-workers.<sup>11</sup> Four of their patients received penicillin alone; 11 had induced malaria fever in addition. Only 2 patients in their series showed diminution of vision, and these patients had received the combined treatment.

It is difficult to draw definite conclusions as to the value of penicillin in these small series of patients, many of whom have been observed for short periods. It would appear from the foregoing studies, however, that the use of penicillin alone is effective in arresting the process in approximately one-half the cases. Since malaria therapy has been shown to be valuable in the treatment of this condition, the use of penicillin alone is not advisable, and a combination of penicillin and fever therapy is probably the treatment of choice. In patients who cannot tolerate fever, however, penicillin is indicated and is superior to other forms of chemotherapy.

#### CONCLUSIONS

The results obtained with the use of penicillin in the treatment of various forms of syphilis of the eye are reported. Penicillin produced little or no immediate response in patients with interstitial keratitis. Clearing of the opacity and subsidence of the inflammation, however, occurred in most patients three to five months after penicillin therapy. Good to excellent vision was finally obtained in 80 per cent of the eyes treated for the initial involvement. Penicillin did not prevent involvement of the second eye in several of our patients, nor did it prevent the appearance of keratitis in 1 patient when given previously for latent syphilis.

Penicillin treatment of 6 patients with acute iritis associated with secondary syphilis resulted in immediate healing of the process and restoration of vision to normal.

Papilledema associated with syphilitic meningitis responded well to penicillin therapy with subsidence of edema and return of normal vision. Eight patients with primary atrophy of the optic nerve were treated with penicillin alone. Four obtained apparent arrest of the process eleven months to two years after completion of treatment.

In general, penicillin appears to be of value in the treatment not only of systemic syphilis but also of the ocular manifestations of this disease. It should be used in combination with fever therapy for atrophy of the optic nerve, but satisfactory results were obtained with penicillin alone in treatment of the other forms of ocular syphilis.

Fort Lauderdale, Fla. (Dr. Benton).

36 Butler Street (3) (Dr. Heyman).

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## DIAGNOSIS OF RETINOBLASTOMA

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Retinoblastoma is an intriguing subject because of the difficulty of early diagnosis, the fearful penalty for delay in treatment, the question of hereditary transmission and the implications of birth control in the affected families. For these and other reasons, the subject of retinoblastoma is presented in the clinical form of 6 case histories, with a description of the ocular signs which led to enucleation in 5 cases and in the sixth, to the unmistakable diagnosis of angiomatosis.

Considering the frequency with which an acute inflammatory reaction leaves a yellow pupillary reflex, which is recognized as the primary sign of retinoblastoma, it is no wonder that eyes are sacrificed; yet, as shown in case 1, the malignant disease may be ushered in by acute congestion of the bulbar conjunctiva, more suggestive of an inflammatory than of a malignant process.

### REPORT OF CASES

CASE 1.—When J. K. was 3 years old she was brought to me with a history that two months before the left eye had become pink and she had been examined under ether anesthesia but that no advice or opinion had been given or treatment instituted.

When I first saw her, the right eye appeared normal on external and ophthalmoscopic examination.

The left eyeball was congested; the pupil measured 6 mm. and was stationary. The details of the iris were obscured, and there was a dull yellow pupillary reflex from a large yellow mass in the fundus, over which the vessels could be traced. The appearance was typical of retinoblastoma, and the eye was enucleated the following day. There were no gross changes in the optic nerve. The globe measured 22 by 21 mm.

Healing was uneventful, and the child was healthy and happy until three months later, when the left eyelids became edematous and puffy, with an evident local orbital swelling. This condition was controlled for a time with roentgen treatments. Four months after the first sign of recurrence the swollen eyelids became ecchymotic. This infiltration of the lids with blood never disappeared. There were no changes in the orbital bones, but the tumor steadily increased in size, becoming a large, vascularized mass. The child died one year after the first signs of the tumor.

*Specimen.*—Section revealed that the angle of the anterior chamber was obliterated. The posterior surface of the lens was covered by a soft, gray layer, several millimeters

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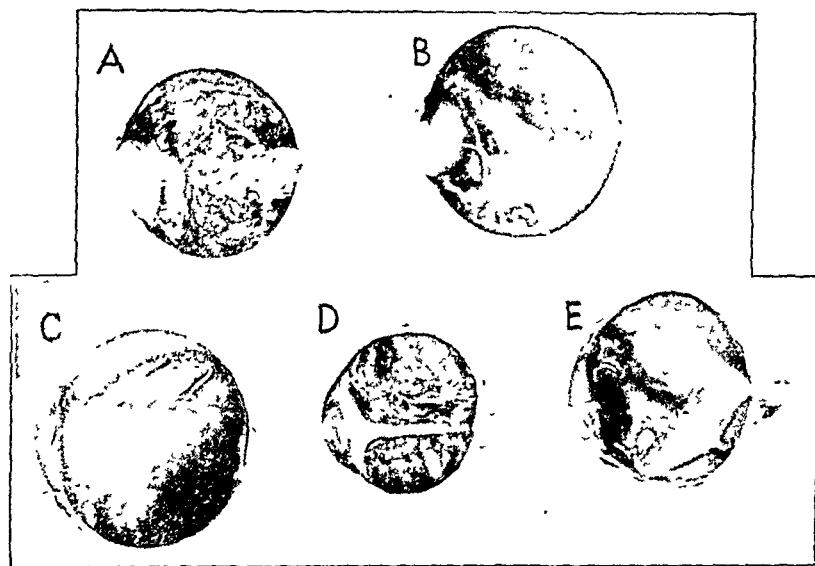
Read at the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 5, 1947.

thick. The retina was transformed into a fungating mass, projecting forward 10 mm. from the papilla (figure, *A*). This mass was soft and yellow gray, with many vessels on it. There was pronounced atrophy of the ciliary processes and of the retina and choroid near the ora serrata.

Microscopically, the tumor was necrotic, with distorted remains of the retina and a delicate vascular stroma, containing dilated capillaries. The tumor cells ranged from ovoid to oat shaped, with relatively large, hyperchromatic nuclei and scanty cytoplasm. The tumor had a perivascular arrangement, which showed a slight tendency to formation of pseudo rosettes. An occasional multinucleated tumor giant cell was noted.

The diagnosis was retinoblastoma.

The case was of interest because of the early inflammatory reaction, which led the parents to delay in bringing the child for diagnosis. With



*A* (case 1), gross specimen of retinoblastoma, showing the fungating mass projecting from the papilla; *B* (case 2), gross specimen, showing the widespread retinoblastoma; *C* (case 3), gross specimen of leukosarcoma, showing a dense, homogeneous tumor above and a soft, flocculent mass below; *D* (case 4), gross specimen of retrolental fibroplasia with extensive intraocular hemorrhage; *E* (case 6), gross specimen of Coats's disease, showing complete detachment of the retina, with a large, thick, yellow infiltration of the retina.

a tumor of such rapid growth, it is doubtful whether anything could have prevented the fatal outcome.

**CASE 2.**—The slower rate of growth and the absence as yet of recurrence is illustrated in this case. The child was first seen when she was 26 months old because something was wrong with the left eye. Nine months before the parents had noticed that the left pupil had a peculiar yellow color, and lately they had noted that the eye rolled about as though she could not see. The child seemed to be in good health and was well nourished.

The right eye was normal.

The pupil of the left eye was 1 mm. larger than that of the right eye, which measured 4 mm. The vessels of the iris were full and prominent, and from the pupil there was a distinct yellow glare. The vitreous was filled with a great tangle of bright shreds. No view of the fundus was possible.

The eye was enucleated. Healing was uneventful, and up to the time of this report, four years later, there has been no recurrence of the tumor.

*Specimen.*—The eyeball was 24 mm. in length and 24 mm. in width and was grossly distended in the anterior half. On transillumination, most of the posterior half was dark.

On section, the anterior chamber appeared shallow; a film of cells covered the posterior surface of the lens and continued as filaments back to the tumor. The sclera was thin. The tumor was a large, cuplike, nodular, yellow mass, varying in thickness from 8 to 3 mm., growing in and on the retina, which was not detached. The optic nerve was not involved.

Microscopic sections showed a cellular tumor arising from the retina and projecting forward into the posterior chamber. The tumor was composed of spindle-shaped to oat-shaped cells with relatively large nuclei and scanty cytoplasm. The cells were loosely arranged, and there was little stroma. A moderate number of capillaries were present. In places, the cells were in palisade arrangement, and in others they tended to form spaces, or pseudo rosettes. Mitoses were infrequent.

The diagnosis was retinoblastoma.

In this case the tumor was large and was growing rapidly in and on the retina. Now, at the end of four years there has been no metastases or recurrence, so that the outcome seems favorable.

CASE 3.—A healthy-appearing boy, aged 8, had as his only complaint a boil on the left eyebrow two weeks ago.

Examination of the right eye revealed a normal condition, with vision of 6/6 and a total refractive error of  $+0.75$  sph.  $+0.75$  cyl., axis 90.

Vision in the left eye was 6/30. The pupil measured 3 mm. and was regular and active. There were many fine, dustlike cells in the vitreous. The disk was slightly oval, but even under the powerful light of the camera it could not be sharply outlined. The veins of the upper half of the fundus were larger than normal, and the superior temporal branch was beaded. The veins in the lower portion were not remarkable. Many reflexes were obtained from the posterior surface of the vitreous. Near the macular region was a yellow, rather sharply defined, irregular, soft, flat area, over which a dilated artery, twice its normal size, passed obliquely down and out. The appearance of the distended vein suggested that usually present in angiomatosis, although no angioma was observed. The soft, yellow area was suggestive of a growth. Palliative measures were taken. No shadow was present on transillumination.

A short time later, the child complained of pain and on examination vision was 6/120 in the left eye, with considerable photophobia. There was an area of hypopyon-like sediment, measuring 1 mm., in the anterior chamber, one bright spot on the nasal side of the pupillary edge of the iris, a larger yellow area behind the iris and a collection of cells on the anterior capsule. The sediment was so fluid that it moved easily on the least motion of the globe. The vitreous was partly filled with a soft, yellow-appearing, somewhat translucent fluid.

The visual field was small, with a large central scotoma.

The eye was enucleated. Transillumination revealed a large, dense shadow, 14 mm. at its widest portion, extending backward 15 mm. from the upper portion of the limbus.

*Specimen.*—On section, the growth which was between the retina and the sclera appeared yellowish gray and homogeneous, measuring 4.5 mm. at its thickest part. There was a large, soft, white-yellow mass in the vitreous, part of, and continuous with, the tumor and loosely attached to it. A 1 mm. ring of pigmentation surrounded the disk.

Microscopic study of a section through the tumor extending posteriorly from the ciliary body showed that it replaced the choroid. A segment of atrophic retina overlay

the tumor. The tumor was composed of short, plump, spindle-shaped cells with large hyperchromatic nuclei, which occasionally exhibited mitosis. The cells were closely packed but in places appeared to be in columns, a pseudoacinous arrangement. The later structure suggested the rosette formation of retinoblastoma. Occasional cells contained brown granular pigment. The production of pigment and the location of the tumor in the choroid made the diagnosis of melanosarcoma quite certain. Because little pigment was being produced, the descriptive term "leukosarcoma" or "a melanotic melanosarcoma" might be applied.

The diagnosis was leukosarcoma of the choroid.

*Subsequent Course.*—The boy remained healthy, without evident symptoms, for three months, at which time a large swelling appeared on the right and another on the left side of the lower jaw. In the region of the latter there was a large, open ulcerating area in the mouth. At the time of writing, the new growths are rapidly enlarging, and the boy has the color of approaching death.<sup>1</sup>

This case is of unusual interest in the appearance of the vessels, which resembled angiomatosis; the fundus picture, which suggested a growth; the pathologic type of the tumor, and the development of multiple metastases.

CASE 4.—The patient was a 4 month old girl, born in the sixth month of pregnancy. For a few weeks prior to consultation, the mother had noted that the left eye was larger than the right and that the baby did not seem to notice things as her two sisters had done at her age.

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1. The patient died five weeks after this report was made.

The anterior chamber of the right eye was shallow. The iris was dark, with a deep yellow-gray reflex visible through the pupil, which measured 3 mm. The pupil of the left eye measured 3.5 mm. and the cornea 11 mm.; the anterior chamber was very shallow, with the same gray-yellow pupillary reflex as that noted in the right eye. The parents were told that the baby was blind as a result of failure of absorption of a membrane, the fibrovascular sheath of the lens, i.e., retrolental fibroplasia.

Six weeks later the left eye had further increased in size, and enucleation was advised. The globe was removed and a glass ball implanted in the capsule of Tenon. Healing was normal. The globe was 17.5 mm. in length.

*Specimen.*—On section, the diagnosis of retrolental fibroplasia was verified, and the cause of the increasing size of the globe was observed to be a large subretinal hemorrhage, extending as a broad red band from the back to the choroid. The anterior chamber was abolished. There was a large anterior corticocapsular cataract. The lens was covered by a firm white membrane, 1.5 mm. in thickness, which extended back, as a white band 1 mm. in width, to the disk. The retina was completely detached.

Microscopically, the red mass consisted of coagulated vitreous with intermingled erythrocytes, without tumor cells.

CASE 5.—This case, which is without pathologic report, is presented, through the courtesy of Dr. Arthur C. Glover, to emphasize the changes observed in case 6. The diagnosis of angiomatosis seems unmistakable, and the changes characteristic of this condition, of a bizarre type, were well shown except for the angioma itself, which was outside the photographic field, in the extreme field visible with the ophthalmoscope.

The right eye was normal. The pupil measured 3.5 mm. and was regular and active. The media were clear. The disk was clearly and distinctly outlined, with a small central excavation. The vessels of the fundus were of normal size and distribution.

The pupil of the left eye measured 3 mm. and was regular and active. After instillation of atropine, the pupil was regular and dilated to 7 mm. with a +2 D. lens;

a large detachment of the retina was outlined, with a sharp, distinct edge, in the lower outer quadrant. The vessels over it gave no reflex. There were several retinal exudates, mostly circumpapillary, consisting of deposits of the circinate type. On the lower outer quadrant above the detachment, the exudate was in yellowish sheets. The disk was outlined with difficulty. The retinal arteries were slightly fuller than normal, and the veins were definitely dilated. About 2 disk diameters to the temporal side of the disk the retinal vessels converged to a point which suggested in form and color a second papilla because it was darker than the surrounding exudate. An angioma was clearly and easily seen far to the temporal side, at axis 180, when the patient looked to the extreme left.

CASE 6—An 8 month old baby did not see as well as the other children, according to the parents. He was born at full term, with a normal delivery, and had had no illnesses.

The pupils measured 3 mm. and were regular and active. After instillation of atropine, the pupils measured 6 mm.; the iris, lens and vitreous appeared normal in each eye, and with a +6 D. lens the disk was faintly visible.

The baby was not seen again for one year, when he was brought to me because of a yellow light from the pupils. A large, deep, yellow glare came from the temporal half of the fundus of each eye. The nasal side was a normal pink.

With the child under ether anesthesia, this reflex was found to be produced by a smooth-surfaced, large, yellow layer without definite boundaries but limited mainly to the temporal half of the retina.

Unfortunately, a year later the right eye became red and painful. The iris was adherent below, and the eyeball was intensely congested, with a great increase in intra-ocular tension.

Enucleation was done because the eyeball was obviously extensively involved and sightless and all previous treatment had been unavailing. Healing was normal, and the child has remained in good health for three years.

The left eye is unchanged; the yellow layer persists unaltered.

*Specimen.*—The right eyeball was 20 mm. long. The retina was completely detached and appeared as a yellow gray, uneven sheet, with many folds.

The pathologic diagnosis, made by Dr. Georgiana Theobald, was that of Coats's disease. The microscopic report follows.

"Slight round cell infiltration (lymphocytes and plasma cells) was present about the conjunctival and episcleral vessels. The cornea appeared normal except for slight round cell infiltration just anterior to the trabeculum and Descemet's membrane. The trabeculae (pectinate ligament) were compressed and contained round cells.

"Anterior Chamber: The angles were obliterated by the root of the iris.

"Iris and Ciliary Body: The iris was fibrotic, with a layer of vascularized tissue on its surface. Over this, and on the posterior surface of the cornea, were many clumps of monocytes and leukocytes (keratitis punctata). The pigment epithelium showed cysts. The ciliary body was solid and cellular.

"Choroid: The choroid was fibrotic and contained round cells. In places the pigment epithelium was proliferating.

"Retina: The retina was entirely detached by albuminous exudate, in which were many bubble, or foam, cells. The retina was atrophic; there were areas of fatty degeneration, as well as deposits of cholesterol crystals, the latter surrounded by foreign body giant cells.

"Optic Nerve: The nerve was atrophic, as evidenced by irregular columns of nuclei.

"The diagnosis was glaucoma secondary to uveitis and retinitis, classifiable as Coats's disease."



It is well known that one form of Coats's all-inclusive disease is frank angiomatosis, and for that reason this case is presented as one in which a yellow reflex was caused not by retinoblastoma, but by the rarer angiomatosis.

In this resume are included three types of the common yellow pupillary reflex complexes; but detachment of the retina, which may at times be confusing, is not discussed, nor is the rare cysticercus in the vitreous considered.

A plea is made for a careful differential diagnosis in order to save the eye when possible and to remove a tumor as soon as the diagnosis is confirmed.

Because of the danger of transmitting retinoblastoma from one generation to another, it is a measure of conservation to advise against future pregnancy in a family in which more than one child has the disease.

I cannot at this time subscribe to the view that 1 case is sufficient to condemn the family to a childless existence.

Dr. John J. Clemmer made the pathologic reports except in case 6.  
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## PRACTICAL APPLICATION OF THE DENERVATED IRIS

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IT HAS LONG been known that the neuroeffector mechanism of denervated autonomic structures becomes sensitive to circulating hormones. This was stated by Cannon in 1939 as a law of denervation.<sup>1</sup>

When in a series of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated.

This phenomenon of sensitization had been observed as far back as 1855, when Budge<sup>2</sup> showed that the sympathetically denervated iris dilates in response to injections of epinephrine so small as to have no effect on the normal iris. Edes,<sup>3</sup> in 1869, corroborated these findings and also showed that the vessels in the denervated ear of the rabbit became intensely constricted when the animal was excited. At that time the reason for this phenomenon was not understood.

In 1904, Meltzer and Auer<sup>4</sup> studied the "paradoxical" pupillary dilation caused by epinephrine and the influence of this drug injected subcutaneously on the eyes of cats after removal of the superior cervical ganglion. Hartman, McCordock and Loder,<sup>5</sup> in 1923, showed that the iris deprived of its sympathetic supply became sensitive to pain, fear and cold and that this effect could be eliminated by bilateral adrenalectomy.

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Funds donated by the Jewish Hospital of Brooklyn aided in the performance of this work.

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toomy. In 1935, Hampel<sup>6</sup> studied the responses of the nictitating membrane of cats after denervation. He showed that the phenomenon of sensitization reached its height in eight days. He also demonstrated the important fact that the sensitization observed after postganglionic sympathectomy is about twice that observed after preganglionic sympathectomy.

These findings have not been without practical value. The phenomenon of sensitization which accompanies postganglionic sympathectomy is now well recognized. The observations of White, Okelberry and Whitelaw<sup>7</sup>; Hampel,<sup>6</sup> and Grant<sup>8</sup> adequately demonstrated that the response of denervated structures to circulating epinephrine and sympathin is more than twice as great after postganglionic as after preganglionic sympathectomy.

White and Smithwick,<sup>9</sup> in their excellent text on the autonomic nervous system, suggested that this phenomenon could explain the poor results of cervicothoracic ganglionectomy in cases of Raynaud's disease of the hand, in contrast with the good results obtained with lumbar ganglionectomy for vasospastic phenomena in the foot. In cases of the latter, after removal of the second and third lumbar ganglions, the postganglionic neurons to the sciatic nerve, which originate in the fourth lumbar and the first, second and third sacral ganglions are still intact. Thus, this operation is a preganglionic sympathectomy. Resection of the inferior cervical and first and second thoracic ganglions destroys most of the cells which give rise to postganglionic fibers to vessels of the arm. This operation is a postganglionic sympathectomy. This important and fundamental fact has been corroborated by many, including Lewis<sup>10</sup>; Simmons and Sheehan,<sup>11</sup> and Foerster.<sup>12</sup>

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Recently, it has been suggested that the denervated iris of the cat may be used as a sensitive indicator of the epinephrine level of the blood (Bender<sup>13</sup>). This investigator noted the minimal amounts of epinephrine required to cause minimal dilation of the sensitized pupil in cats anesthetized with ether and "pentobarbital."

It has been my experience that the denervated iris of the cat is too sensitive an indicator of the epinephrine content of test solutions. The mere act of injection in nonanesthetized animals causes an output of epinephrine which far exceeds the small amounts usually tested for. The attempt to anesthetize these animals causes enormous amounts of epinephrine to be produced (see experiment 1). Stimuli, such as the crack of a gun, a bark or a feint at striking, all cause dilation of a normal pupil. Thus, so much epinephrine is produced that a reaction is obtained not only in the denervated iris but also in the normal, non-sensitized pupil. Nevertheless, one can gain valuable information as to how long certain stimuli cause a heightened level of epinephrine in the blood to exist. For example, if a stimulus is adequate to cause dilation of a normal pupil (as well as the sensitized pupil, of course), one can get some idea of the epinephrine level produced by this stimulus if one observes the differences in dilation of the two pupils and, more important, the difference in time required for the pupils to return to their original sizes.

It is assumed, of course, that the indicator of a normal epinephrine level in the blood is not the return of the nonsensitized pupil to its normal size (after a stimulus), but, rather, the return of the sensitized pupil, as indicated by the fact that very small increases in the epinephrine level will produce dilation of the sensitized pupil and may yet be too small to cause the normal pupil to dilate.

Practical application of these principles is demonstrated in the experiments which follow.

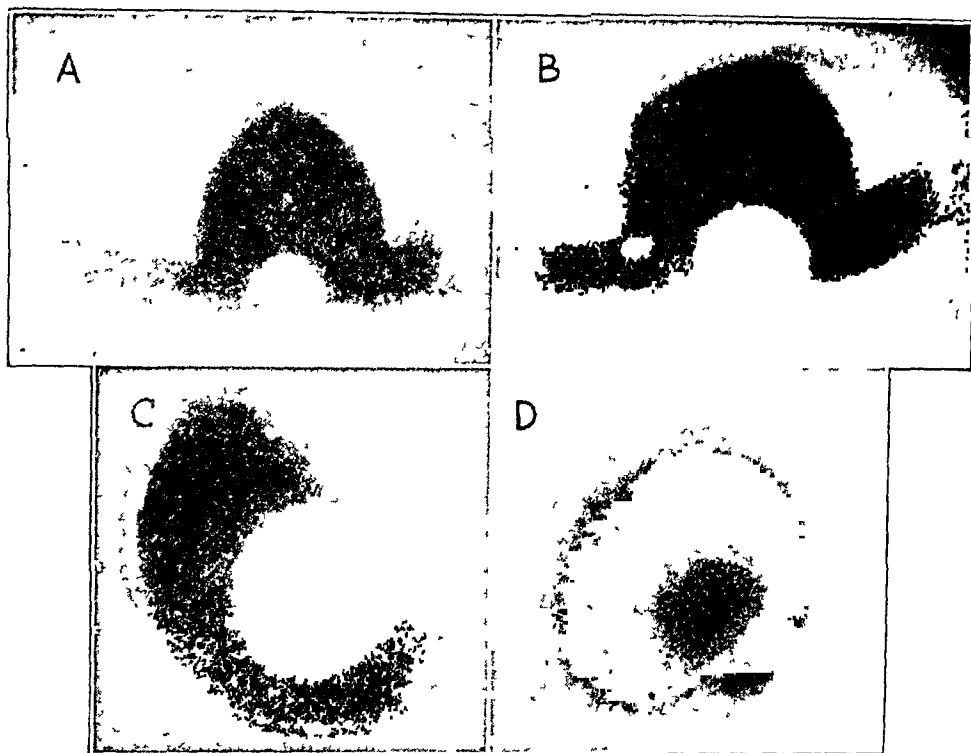
#### EXPERIMENTAL STUDY

EXPERIMENT 1.—Cats were chosen because of the high development of the sympathetic nervous system in these animals. Both male and female animals were used, the weights ranging from 4.8 to 7.2 pounds (2.4 to 3.6 Kg.). Postganglionic cervical sympathectomy was performed on the right side of each of 8 animals. The nerve section was performed 2 to 4 mm. superior to the superior cervical ganglion. None of the branches of the ganglion were cut. The nictitating membrane was removed bilaterally. Horner's syndrome was apparent within ten seconds after the sympathectomy in all animals, and the law of denervation was manifested before the tenth postoperative day, but in none of the animals did the phenomenon of

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13. Bender, M.: Sensitized Pupillary Dilator and Facial Muscles as Indicators of Sympathetic and Parasympathetic Substances in the Blood, *Proc. Soc. Exper. Biol. & Med.* **39**:62, 1938.

sensitization appear before the second day. This observation is in agreement with the findings of other investigators. The sensitivity did not appear to be an "all or none" phenomenon. There were stages of sensitization, the height occurring on the fourth to the seventh day. This was manifested by a "paradoxic anisocoria." The pupil on the side of operation, which was small as a result of the sympathectomy (Horner's syndrome), was now larger than the normal pupil. The palpebral fissure on the side of operation became wider than its fellow. In all cats a prominent exophthalmos took place after operation. However, during the height of sensitization (four to seven days after operation) most of the cats (6) showed exophthalmos.



In taking the photographs of the pupil, infra-red illumination was used, since it does not alter the size of the pupils. Only the pupil is shown; the lids are not included. The round, white corneal reflexes of the infra-red lights are prominent. The horizontal black shadow at the lower margin of the pupil is the shadow cast on the eye of the lower lid.

*A* shows the denervated pupil at rest. It is small, owing to the Horner syndrome. *B* shows the normal pupil at rest, and *C*, enlargement of the denervated pupil with the animal under ether excitement. Exophthalmos is present, hence there is no shadow of the lower lid. *D* shows enlargement of the normal pupil under ether excitement.

These changes could be observed while the cat was at rest, and under no emotional stress, during this period. After the seventh postoperative day the picture reverted to the Horner syndrome seen immediately after the sympathectomy. Pupillographic changes were noted in these animals, and they will be the subject of another paper.

The present studies were made on these animals two to five months after operation. The animals still showed a Horner syndrome on the right side, with

no evidence of regeneration. They appeared at this time exactly as they did after the seventh postoperative day.

Each cat was placed in a cat box with the head protruding. Photographs were taken of the state of the pupils after fifteen minutes' rest in the box (figure, *A* and *B*). The animal was then subjected to ether anesthesia. The normal pupil dilated as the cat went into the stage of excitement, but the opposite pupil dilated maximally (figure, *C* and *D*). The Palpebral fissure widened, and exophthalmos

TABLE 1.—*Cats Subjected to Postganglionic Sympathectomy*

Cat No.	Duration of Ether Anesthesia, Min.	Time for Denervated Pupil to Become Normal, Min.
18	3	45
27	3	50
22	2½	62
26	2	71
24	3	61
25	2½	63
9	3	65
16	2	53
		Average 59

was present in all 8 cats. After about two to three minutes of excitement, the animal went into the first plane of surgical anesthesia (stage 3). The dilated normal pupil contracted. Anesthesia was discontinued. The sympathectomized pupil remained large. The time for this pupil to return to its preanesthetic size was noted, an average of fifty-nine minutes being required (table 1).

It has been stated that there is some sensitivity of structures after preganglionic sympathectomy. The sensitivity is about one-half that seen after postgang-

TABLE 2.—*Cats Subjected to Preganglionic Sympathectomy*

Cat No.	Duration of Ether Anesthesia, Min.	Time for Denervated Pupil to Become Normal, Min.
20	2	36
28	3	30
21	3	26
15	2½	28
29	2½	39
		Average 32

lionic sympathectomy. Therefore, to check the results described, 5 animals were selected for preganglionic section on the right side. The nerve was cut 1 to 2 cm. inferior to the superior cervical ganglion. Horner's syndrome was again apparent in less than ten seconds. The experimental work with ether was performed exactly as described for the animals undergoing postganglionic sympathectomy. The work was done two to four months after operation. The period of sensitization seen four to seven days after operation was never observed in these animals. However, ether

anesthesia was capable of causing excitement to the degree that the pupil on the side of operation became larger than the pupil on the normal side, but never as large as the pupil on the side of postganglionic sympathectomy. The time for the right pupil to return to its original size was noted. From the results in table 2, it is seen that this pupil takes less time to return to its preanesthetic state than the pupil with postganglionic sympathectomy. It required an average of thirty-two minutes for the former and fifty-nine minutes for the latter.

*Comment.*—It is generally known that the stage of excitement during ether anesthesia is accompanied with a great outpouring of epinephrine. In normal persons equal pupillary dilation occurs. During the first plane of stage 3 the pupil becomes smaller, accompanied with a drop in the level of epinephrine. The pupil becomes larger again as anesthesia deepens, but this is due to direct sphincter paralysis. It is thought that the level of epinephrine begins to approach normal while the patient is in the first plane of surgical anesthesia. However, does the epinephrine level become normal? The question then arises: Does ether itself cause production of epinephrine? I set out to prove that ether is sympathomimetic, i.e., that ether causes production of epinephrine not only in the stage of excitement of anesthesia but during the third stage, which follows.

With this in mind, the results are analyzed. In the first plane of stage 3, the epinephrine level is above normal, since the sensitized pupil is maximally dilated; but it is decreasing, since the normal pupil has contracted. After the discontinuance of anesthesia, an average of fifty-nine minutes was required for the sensitized pupil to return to its original size. It is repeated that this is the interval required for the epinephrine level of the blood to assume its normal value. Thus, the amount of epinephrine produced during the stage of excitement required fifty-nine minutes to be metabolized.

The work done with the cats subjected to preganglionic sympathectomy serves as a check on these observations. Since the sensitization in these animals is only about half that in the cats undergoing postganglionic sympathectomy, the difference between the pupils would not be expected to be as large, and the sensitized pupil would be expected to return to its normal size sooner than the pupil after postganglionic sympathectomy. In all cases this assumption was borne out. Consequently, normal size of the sensitized pupil with preganglionic sympathectomy does not indicate a normal epinephrine level, since this pupil is less sensitive than the pupil with postganglionic sympathectomy.

Even small increases of epinephrine for extremely short intervals can be detected. By utilizing the pupillographic method developed by O. Löwenstein, one can demonstrate by means of serial photographs of the pupil the length of time necessary for the dilated sensitized pupil to return to its usual size, even if it is only a fraction of a second. Stimuli such as

the crack of a gun, a laugh or a shout cause increased epinephrine levels in the blood. Needless to say, the denervated iris of the cat indicates not how much, but, rather, for how long the epinephrine level is increased. However, it is reasonable to assume that the length of time it is increased is a function of the height of the increase.

EXPERIMENT 2.—It will be shown that ether itself is sympathomimetic. It is not correct to assume that once a patient reaches the first plane of surgical anesthesia epinephrine is no longer being produced. However, the rate of production in stage 3 is much less than that in stage 2.

The animals in the first experiment were used. The same conditions prevailed. Each animal was given ether sufficient to carry it through the stage of excitement into the second plane of surgical anesthesia. At this point the normal pupil contracted, after having dilated during the stage of excitement. The sensitized pupil, which had dilated maximally in the stage of excitement, showed no change. The animals were then maintained in the second plane of stage 3. In each animal the sensitized pupil became slightly smaller than its size during the stage of excitement. However, it never approached its preanesthetic size, and in no cases did it become as small as the normal pupil, even after four to five hours of anesthesia.

*Comment.*—If no epinephrine had been produced after the stage of excitement, the experiment would have proceeded like the first one; i.e., the sensitized pupil would have returned to its preanesthetic size in about fifty-nine minutes in spite of the fact that the ether was still being given. This demonstrates that production of epinephrine proceeds as long as ether enters the blood stream. Thus, epinephrine is being produced continuously throughout any operation with ether anesthesia.

In 1912, Elliott<sup>14</sup> noted that ether caused a reduction in the epinephrine content of the adrenal glands. Bhatia and Burn,<sup>15</sup> in 1933, reported that ether caused a general stimulation of the sympathetic nervous system, manifested by the characteristic response of the organs innervated. The hypothalamus may be the seat of this stimulation. Barbiturates, which act on nuclei of the brain stem, are known to prevent this production of epinephrine. Barbiturates given intravenously or directly into the hypothalamus are effective in eliminating cardiac arrhythmias in chloroform anesthesia attributed to sensitivity to epinephrine (Dikshit<sup>16</sup>). It follows, then, that ether is a good anesthetic in cases of hyperinsulinism because of the production of epinephrine. However, "amytal" can prevent ether hyperglycemia (Banerji and Reid<sup>17</sup>).

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14. Elliott, T. R.: The Control of Adrenalin Secretion, *J. Physiol.* 64:274, 1912.

15. Bhatia, B. B., and Burn, J. H.: Action of Ether on the Sympathetic Nervous System, *J. Physiol.* 78:257-270, 1933.

16. Dikshit, B. B.: Production of Cardiac Irregularities by Excitation of Hypothalamic Centers, *J. Physiol.* 81:382-394, 1934.

17. Banerji, H., and Reid, C.: Adrenals and Anesthetic Hyperglycemia, *J. Physiol.* 78:370-380, 1933.



The toxic effect of ether on the heart is relatively slight. Chloroform is twenty-five to thirty times as toxic. Although ventricular fibrillation is commonest during chloroform anesthesia, Guedel<sup>18</sup> pointed out that this must be considered a potential danger in every case of anesthesia, no matter what agent is used. He cited several cases which illustrate the relation of ether and epinephrine to ventricular fibrillation. Cyclopropane not uncommonly sensitizes the heart to epinephrine. Therefore, all possible measures to keep production of epinephrine at a minimum must be taken. Many anesthetists use small amounts of ether to eliminate arrhythmias during cyclopropane anesthesia. From what has been shown here regarding the sympathomimetic effect of ether, this constitutes a hazardous procedure.

EXPERIMENT 3.—A third experiment was finally performed. Three grains (0.19 Gm.) of "sodium amytal" was given intraperitoneally to each of the 8 ani-

TABLE 3.—*Relation of Barbiturates to Production of Epinephrine*

Cat	Time for Denervated Pupil to Become Normal, Min.*
18	7
27	5
22	10
26	8
24	9
25	7
9	10
16	9
	Average 8

\*Readings were begun one hour after intraperitoneal injection of "sodium amytal."

mals with postganglionic sympathectomy. One hour later ether was administered to the animals. In no animal did the sensitized pupil remain dilated for more than ten minutes after the ether was discontinued, in the first plane of stage 3 (table 3).

*Comment.*—These observations prove that barbiturates will inhibit the production of epinephrine. Morphine will not prevent hyperactivity of the sympathetic nervous system. Consequently, since epinephrine is produced throughout the course of anesthesia, since ventricular fibrillation due to sensitivity to epinephrine may occur anywhere in anesthesia and since barbiturates are capable of inhibiting production of epinephrine, it is maintained that a barbiturate should be included as part of the medication before ether anesthesia.

18. Guedel, A.: *Inhalation Anesthesia*, New York, The Macmillan Company, 1944.

## SUMMARY

Contributions to the development of the law of denervation are cited.

The denervated iris of the cat is too sensitive an indicator of the epinephrine content of foreign solutions, but may be used as a very sensitive indicator of the increase in the epinephrine level of the blood provoked by any stimulus exerted on that animal.

There may be an increase in the epinephrine content of the blood without dilation of the normal pupil. In fact, relatively large increases in the epinephrine level are required before the normal pupil begins to dilate.

The stage of excitement of ether anesthesia causes an output of the epinephrine; the amount produced required 8 cats an average of fifty-nine minutes to metabolize it.

Ether is sympathomimetic and causes production of epinephrine even after the stage of excitement (stage 2) of ether anesthesia.

Barbiturates are capable of inhibiting the production of epinephrine due to ether anesthesia, and their use is therefore recommended as valuable preanesthetic medication whenever ether anesthesia is used.

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## CLINICAL ANISEIKONIA

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FOR THE PURPOSE of investigating the value of iseikonic glasses, a study was made of the 1,027 patients examined for aniseikonia at the Institute of Ophthalmology of the Presbyterian Hospital, New York, between December 1936 and December 1941.<sup>1</sup> These patients were referred for the examination by ophthalmologists and characteristically were those whose complaints bore a close relation to the use of the eyes and on whom the usual ocular therapeutic measures had been tried without relief being obtained. At the conclusion of the examination of the patient a report of the result was sent to the physician who had referred the patient. The trial of iseikonic glasses was not advised merely because aniseikonia was demonstrated, but the opinion was given that a factor was revealed by the examination which had not previously been corrected and which it was possible to correct. The decision whether iseikonic glasses were to be prescribed was left to the physician who had referred the patient for the examination.

Whenever possible, the refractive correction reported by the referring ophthalmologist was used as the basis of the test for aniseikonia. This was done to eliminate a change in the refractive correction influencing the result. In the small number of cases in which it was found necessary to make a change, it was usually possible to allow the patient to wear the correction both with and without the iseikonic factor in order that an accurate interpretation of the result could be made. This was accomplished by the almost routine use of trial or temporary lens sets, which consisted of the usual power lenses in the frame, the size, or aniseikonic, correction being added by fit-over lenses accurately adjusted over one or both eyes.

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Miss Catherine Rittler gave technical assistance in this study.

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From the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, and the Institute of Ophthalmology of the Presbyterian Hospital in the City of New York.

1. Ames, A.; Gliddon, G. H., and Ogle, K. N.: Size and Shape of Ocular Images: Methods of Determination and Physiologic Significances, *Arch. Ophth.* 7:576 (April) 1932.

The attempt was made to eliminate the effect of the extraocular muscle balance in the estimation of the results. In no case was a prismatic correction added to the iseikonic prescription when it had not been previously included in the correction worn by the patient. In no case was the strength of the prismatic correction already worn by the patient changed, except that in 11 instances small prismatic corrections were omitted in the iseikonic lenses prescribed for patients in the group showing improvement, when they were not considered a necessary component of the prescription and investigation had revealed that they were not a factor in the relief of the symptoms of which the patient complained.

It was recognized that the correctness of the patient's conclusion as to the relief of symptoms was difficult to estimate, and every effort was made to reach an accurate evaluation. This was done by direct report from the patient and from the physician who referred the patient for the examination. In some instances, while relief of symptoms was reported by the patient, the iseikonic lenses were not worn; in others, the correction was worn, even for years, in spite of the fact that no benefit was received. The influence of psychotherapy as the result of a rather formidable examination and the prescription of a radically new type of correcting lens was recognized. This, presumably, was the explanation of the cases in which relief from the symptoms of which the patient complained was obtained as soon as the iseikonic glasses were worn, but was followed by a gradual return of the symptoms in the course of a few weeks or months, during which time the correction continued to be worn.

A preliminary analysis of the results obtained was made on the basis of an interval of from three to six months after the prescription of the iseikonic glasses. Of the 1,027 patients examined, 527 showed demonstrable aniseikonia, and of these, there were 463 who received the correction for whom the result could be estimated. Of those receiving the glasses, 365 (79 per cent) were considered to have been relieved of all or a part of their symptoms, and 98 (21 per cent) were not benefited.

In 1946, from five to ten years after the original estimate was made, a questionnaire was sent to each of the 365 patients who were considered in the original analysis to have been benefited. Each patient was asked: "1. Are you still wearing the iseikonic glasses? 2. If you are no longer wearing them, how long did you continue to wear them? 3. Did you consider that you had been helped by them or not?" Replies were received from 206 of the original series of 365 patients. Of the patients who answered, 152 stated that they had been helped by the iseikonic glasses, and 54 said that they had not been benefited. In the preliminary analysis, 98 patients were classified as not benefited by the iseikonic

glasses, and 54 more were revealed by the questionnaire not to have been helped; thus, 152 of the original series were not benefited, and 152 reported improvement from use of the glasses. Therefore, of a total of 304 patients, after five to ten years, 50 per cent were benefited and 50 per cent were not benefited (table 1).

TABLE 1.—*Results of Wearing Aniseikonic Correction in a Series of 463 Patients*

Patients examined for aniseikonia (1936-1941).....	1,027			
Prescriptions given.....	527			
Prescriptions filled.....	463			
Results of Wearing Prescription				
	Three to Six Months		Five to Ten Years	
	No.	%	No.	%
Improvement .....	365	79	152	50
No improvement .....	98	21	152	50
	463		304	

TABLE 2.—*Symptoms in Series of Patients with Aniseikonia*

	Entire Series (463)		Three to Six Months				Five to Ten Years			
			Improvement (365)		No Improvement (98)		Improvement (152)		No Improvement (152)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Fatigue, near vision	386	83	315	87	71	72	116	76	104	68
Headaches	307	66	238	65	69	70	92	61	103	68
Pain or discomfort	243	52	182	50	61	62	72	47	85	56
Fatigue, distance	236	51	186	51	50	51	73	48	69	45
Photophobia	216	47	172	47	44	45	55	36	64	42
Burning and itching	111	24	91	25	20	20	24	16	33	22
Panorama sickness	100	22	75	20	25	26	25	16	36	24
Blurring	86	19	68	19	18	18	16	11	25	16
Vertigo	69	15	48	13	21	21	15	10	31	20
Nausea	65	14	44	12	21	21	14	9	28	18
Lacrimation	42	9	30	8	12	12	6	4	16	11
Confusion	35	8	23	6	12	12	9	6	14	9
Pulling sensation	18	4	11	3	7	7	4	3	13	9
Slow reading	14	3	13	4	1	1	6	4	2	1

The records of the patients who had received aniseikonic corrections were studied to determine, if possible, what factors might suggest the presence of aniseikonia and, if present, whether its correction might result in benefit to the patient.

Analysis was made by sex, age and vocation of the cases in which the aniseikonic correction was tried. There were approximately as many male (46 per cent) as female subjects (54 per cent). The youngest patient examined was 5 years of age, and the oldest 70, with the fourth and

fifth decades having the largest numbers and with the third and sixth decades almost as well represented. The actual vocations were of no significance except that intense use of the eyes in the range for near vision, and less frequently in the range for distance, was common to all.<sup>2</sup>

In an endeavor to determine whether any symptom was of significance, a classification was made of the number of patients and the percentage of the group under consideration who complained of the symptom. There was a close correspondence in the incidence of the symptoms not only for the entire series but for both the groups showing improvement and the groups not showing improvement. The nature of the symp-

TABLE 3.—*Refractive Errors of Patients with Aniseikonia*

	Entire Series (463)		Three to Six Months				Five to Ten Years			
			Improve- ment (365)		No Im- provement (98)		Improve- ment (152)		No Im- provement (152)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Isometropia										
Emmetropia	10	2	10	3	0	0	6	4	2	1
Equal error	41	9	35	10	6	6	10	7	13	9
Anisometropia, opters										
0.12—0.25	156	34	126	34	30	31	65	43	48	32
0.37—1.00	164	35	120	33	44	45	42	28	61	40
1.12—2.50	60	13	49	13	11	11	19	11	20	13
2.62 and over	32	7	25	7	7	7	10	7	8	5

tom of which the patient complained appeared to be of no significance in the estimation of the presence of aniseikonia. These symptoms were similar to those for which a patient seeks assistance from the ophthalmologist. The only significant factor was an association between use of the eyes and the difficulty of which the patient complained<sup>3</sup> (table 2).

As anisometropia has been thought to contribute to the presence of aniseikonia, the records of the patients receiving aniseikonic corrections were studied in order to compare the refractive errors of the two eyes by estimating the maximum difference of the dioptric correction in whatever meridian this occurred as a basis of the classification of the anisometropia. In the entire series there were 51 patients (11 per cent) with isometropia, while 207 (45 per cent) had a difference of less than 0.37 D. in the refractive error of the two eyes. In only 32 patients (7 per cent) was there a difference greater than 2.50 D. The close correspondence of the incidence of anisometropia in the entire series and in the two

2. Berens, C., and Loutfallah, M.: Aniseikonia: Study of Eight Hundred and Thirty-Six Patients Examined with Ophthmo-Eikonometer, *Am. J. Ophth.* 22:625 (June) 1939.

3. Burian, H. M.: Clinical Significance of Aniseikonia, *Arch. Ophth.* 29:116 (Jan.) 1943.

groups of patients with and without improvement from the aniseikonic correction suggested that the relation between anisometropia and aniseikonia<sup>4</sup> was not close (table 3).

The magnitude of the refractive errors did not seem to influence the results, as errors ranging from  $-9.50$  to  $+13.50$  D. were included in

TABLE 4.—*Distribution of Magnitude of Aniseikonic Correction in Patients Benefited and in Those Not Benefited by Correction*

Per Cent	Three to Six Months			Five to Ten Years		
	Improvement (365)			Improvement (152)		
	Over All	Meridional	Mixed	Over All	Meridional	Mixed
0.50—1.00	65	61	5	34	30	3
1.25—2.00	41	73	70	18	29	30
2.25—3.00	3	7	26	1	4	3
3.25—4.00	1	1	7	0	0	0
4.25—5.00	1	1	2	0	0	0
5.25 and over	1	0	0	0	0	0
Per Cent	No Improvement (98)			No Improvement (152)		
	Improvement (365)			Improvement (152)		
	Over All	Meridional	Mixed	Over All	Meridional	Mixed
0.50—1.00	17	26	2	27	34	4
1.25—2.00	8	15	19	14	28	29
2.25—3.00	0	2	5	0	2	8
3.25—4.00	0	1	2	0	1	4
4.25—5.00	0	0	0	0	0	0
5.25 and over	1	0	0	1	0	0

TABLE 5.—*Incidence of Magnitude of Aniseikonic Correction in Patients Who Were Benefited and in Patients Who Were Not Benefited by Iseikonic Correction*

Per Cent	Three to Six Months		Five to Ten Years	
	Improvement (365)	No Improvement (98)	Improvement (152)	No Improvement (152)
	Per Cent	Per Cent	Per Cent	Per Cent
0.50—1.00	36	46	43	42
1.25—2.00	50	43	49	47
2.25—3.00	10	7	7	7
3.25 and over	4	4	1	4

the series and surprisingly satisfactory results were obtained in persons with insignificant or no refractive errors.<sup>5</sup> It was my impression that neither the magnitude of the refractive errors nor the anisometropia was significant in the relief of symptoms with the use of iseikonic glasses.

A study of the magnitude of the aniseikonic correction included in the prescriptions revealed that the great majority of errors, when over-all

4. Carleton, E. H., and Madigan, L. F.: Relationships Between Aniseikonia and Ametropia, from Statistical Study of Clinical Cases, *Arch. Ophth.* 18:237 (Aug.) 1937.

5. Hughes, W. L.: Aniseikonia in Emmetropia, *Am. J. Ophth.* 20:887 (Sept.) 1937.

or meridional, were between 0.50 and 2.00 per cent, and when a combination of the two types, were between 1.00 and 3.00 per cent (table 4). Comparison of the incidence of the magnitude of the aniseikonia in the patients who were benefited and in those who were not benefited did not reveal any significant differences (table 5). It has been my practice to prescribe as low as 0.5 per cent either as an over-all or as a meridional correction, and this small amount has been as important in giving relief as has the use of larger corrections. The finding of the theoretic size difference as indicated by the amount of the anisometropia has not been commonly observed.

The reports of the 206 patients who answered the questionnaire were studied with regard to the length of time the iseikonic glasses had been worn. Of the 152 who had been benefited by the correction, 3 had ceased to wear the glasses within five years, and the remaining 149 had been wearing the correction from five to ten years. Of the 54 who reported that they had not been aided by the iseikonic glasses, 23 discontinued wearing the glasses within one year, 10 within two years and 16 more within five years, while 4 persons finally discarded the glasses after wearing them from five to ten years (table 6).

TABLE 6.—*Relation of Length of Time Iseikonic Glasses Were Used to Improvement*

No. of Years	Improvement	No Improvement
1 .....	0	23
2 .....	2	10
3 .....	1	5
4 .....	0	8
5 .....	53	3
6 .....	44	1
7 .....	22	2
8 .....	7	1
9 .....	19	0
10 .....	4	1
Total .....	152	54

#### CONCLUSIONS

1. No symptoms are characteristic of aniseikonia, but symptoms associated with use of the eyes not relieved by the usual ophthalmic therapeutic measures may be due to it.

2. The presence of aniseikonia cannot be anticipated on the basis of anisometropia or the magnitude of the refractive error.

3. It is not possible to anticipate whether the correction of aniseikonia will aid the patient.

4. Iseikonic glasses should be used only for the relief of symptoms, and then only after the failure of the usual ocular therapeutic measures to give relief.

5. Although the number of patients aided by iseikonic glasses is small, these patients are entitled to all the assistance that can be given them.



## MEDICAL VERSUS SURGICAL TREATMENT OF GLAUCOMA

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Although many textbooks state that the treatment of glaucoma is surgical regardless of the stage in which it is encountered in actual practice, this is not true. I am in accord with most of my associates, who treat every patient with glaucoma medically until such time as control of intraocular pressure is no longer maintained at a limit at which visual acuity and the visual fields may be conserved.

### ACUTE CONGESTIVE GLAUCOMA

It is agreed by all ophthalmologists who have extensive experience with glaucoma that the acute congestive type should be treated with tension-reducing drugs for at least twenty-four hours, combined with sedatives sufficient to reduce pain and induce sleep. If the commonly used tension-reducing drugs are not effective within twenty-four hours, a basal iridectomy should be performed. If, however, the repeated use of physostigmine salicylate, for instance, 1 drop of a 1 per cent solution every ten minutes for six doses, followed by instillation of pilocarpine nitrate (1 per cent) every hour, or of methacholine chloride (20 per cent) and neostigmine methylsulfate (5 per cent), 1 drop every ten minutes for six doses, followed by pilocarpine nitrate (1 per cent) every hour, is effectual in reducing the intraocular pressure to such an extent as to bring about the return of normal vision, surgical intervention may be deferred.

I have treated a number of patients with acute congestive glaucoma without surgical intervention, and they have had only one attack. At present I have under my care at least 6 patients who have had one episode of acute congestive glaucoma and for whom surgical treatment has not been necessary. They have been carried along with medical treatment over a period of years. The oldest of these, a woman of 65, lost one eye from glaucoma following operation by another surgeon

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and refused to permit operation on the other eye. She has normal vision in the remaining eye and has had no attack of acute glaucoma in this eye.

A second patient, aged 50, who had an acute attack of glaucoma, was prepared for operation at the Wills Hospital. However, the tension and vision returned to normal while he was in the hospital, after three days of medical treatment, and he then refused to have the operation. Vision and intraocular tension are still normal, and the fields of vision have been only slightly disturbed, after a lapse of four years.

On the other hand, there are innumerable cases of acute glaucoma in which operation has been performed and the tension reduced, but the visual acuity has been reduced also. I have no record of a single case, either in private or in clinical practice, in which a surgical procedure for acute glaucoma has not in itself resulted in some loss of vision. True, surgical measures in cases of acute congestive glaucoma reduce tension and restore vision, sometimes from complete blindness to normal acuity. This return of normal vision, however, is only temporary, for the surgical procedure has produced an abnormal condition, hastening opacity of the lens. Nevertheless, surgery is the only means at one's command when medical treatment with tension-reducing drugs fails. I wish to stress that the use of tension-reducing drugs should be exhausted before surgical intervention is contemplated.

With the introduction of di-isopropyl fluorophosphate ("DFP") a new remedy has been added, which may defer operative measures.

There are many cases of acute congestive glaucoma in which the acute stage may be converted into a quiescent stage, a condition not to be confused with chronic simple glaucoma. In other words, the acute wet type of glaucoma is completely resolved. The eye becomes dormant and normal in function with the use of mild miotics and enters a normal phase, or interlude, in which there are no signs of glaucoma for many years. Of course, unusual excitement may disturb that interval of quiescence and bring about another acute attack. The patient, however, mindful of this possibility, can maintain his equanimity by anticipating an emotional upset and can use miotic drugs during the period of his emotional excitement. But once a patient has glaucoma, he always has glaucoma. At least he is always a patient; just as is the patient with hypertension and the patient with diabetes.

#### CHRONIC CONGESTIVE GLAUCOMA

While acute congestive glaucoma is the very wet, spongy type, chronic congestive glaucoma is spongy to a less degree. The latter is not so fulminating in onset or so dramatic in its appearance. Although in

rare cases the acute wet type may lapse into the chronic congestive type, the latter oftenest has a history all its own. Its onset may be characterized by headaches, periodic disturbance of vision, presence of halos around lights, redness of the eye, dilated pupils (one or both) and difficulty in reading. These symptoms are sufficient to attract the attention of the patient and the examining physician.

In the acute attack, the tension may vary from 40 to 90 mm. or above, whereas in the chronic congestive type the tension varies only in the lower range of 20 to 60 mm. (These figures are not actual but approximate and should be considered only as a guide.)

TABLE 1.—*Data on 5 Eyes with Chronic Congestive Glaucoma In Which Iridectomy Was Performed\**

Case No.	Years Treated	Tension, Mm.	Gains in Vision
1	10	66 to 25	Hand movements - 3/60
2	½	60 to 23	Hand movements - 6/15
3	7	45 to 20	2/60 - 6/9
4	4	56 to 26	2/60 - 6/21
5	6	56† to 22‡	2/60† - 6/12‡

Interpretation: Congestive glaucoma does best under medical treatment, followed by surgical and then medical treatment.

\*These 5 cases of chronic congestive glaucoma, and the 47 cases of chronic simple glaucoma listed in table 2, form a series of 52 cases of glaucoma on active file in my clinic at Wills Hospital; analysis was made by Dr. J. Eisenberg, clinic assistant.

†First values.

‡Last values.

Treatment of the chronic congestive type of glaucoma is medical, with use of tension-reducing drugs, such as pilocarpine, pilocarpine and physostigmine, physostigmine alone or di-isopropyl fluorophosphate. In cases of this type the medical treatment may be carried on over a much longer period than in cases of the acute wet type, because the increased tension is not so promptly damaging as in the former. Also, with the chronic congestive type there is ample time for compensation in that the eye may tolerate intraocular pressures ranging from 20 to 40 mm. without the eyesight necessarily being affected and without serious changes in the visual fields. Control of the intraocular tension in this category of cases does not mean a reduction to normal, which is believed to be 20 mm. of mercury, but consists in reduction to a degree which the eye in question will tolerate. In like manner, hypertensive patients may feel uncomfortable if their blood pressure is reduced to 120 mm., and diabetic patients may be uncomfortable if their blood sugar is reduced to an arbitrary normal.

One must reevaluate one's ideas as to normal pressure in a normal eye and the pressure tolerated by a glaucomatous eye. It is an error to reduce the pressure of a pathologic eye to the normal for a normal eye; just as it is wrong to reduce the blood pressure of a hypertensive patient to the normal for a normal patient, or the blood sugar of a patient with chronic diabetes to the normal blood sugar for a normal person.

Many patients with chronic congestive glaucoma may be maintained under medical treatment for months and years. The congestive, or mildly wet, stage may be transferred to a dry, or intermittent, period, in which the halos are no longer seen, vision has improved, the headaches have disappeared and the visual fields have remained sufficiently large for the purpose of the individual patient.

By far the majority of my private patients with acute or chronic congestive glaucoma are women. In the younger age group, from 40 to 50 years, occur the larger number of cases of acute congestive glaucoma, and the younger portion of the old age group, from 50 to 60 years, contributes the greater number of cases of chronic congestive glaucoma.

Medical treatment consists in the use of pilocarpine nitrate (1 per cent) in a buffered solution three times a day, the instillations being gradually reduced to two a day, and then one a day, as the symptoms recede. Should there be an intermittent flare-up of the condition, I recommend pilocarpine nitrate (1 per cent) three times a day and 1 drop of physostigmine salicylate, 1 per cent (buffered), at bedtime. When the patient no longer complains of visual symptoms and is free from headaches, I reduce the strength of the solution of pilocarpine to 0.5, or even 0.25, per cent, to be used once, at bedtime.

There are times when patients discontinue medication for reason of illness or family difficulties which interfere with the convenient use of the drug, and I find that the lapse of months without miotics has done no great damage in cases of chronic congestive glaucoma during the quiet period, or, in other words, that period in which compensation of intraocular pressure finds a satisfactory level.

If the patient has repeated exacerbations of increased intraocular pressure with symptoms, despite medical treatment, operation should be performed.

#### CHOICE OF OPERATION

The choice of operation for chronic congestive glaucoma depends, in a measure, on the amount of vascular injection of the eye at the time of operation. A fiery red, spongy eye requires basal iridectomy. When the eye is only mildly injected, and there are no signs of atrophy of the iris, an iridencleisis should be performed.

In no circumstances do I advise an Elliot trephination on an acutely inflamed, or even a partially inflamed, eye. It must be kept in mind that every surgical procedure on an acutely or a moderately inflamed eye results in definite damage from the operation itself. I repeat this statement because of its importance.

However, if one decides to operate in a case of chronic congestive glaucoma during the quiet interlude because vision is being lost and the fields of vision are rapidly being cut down, I recommend the Eliot trephination. My greatest objection to this operation at any time, however,

is that it is difficult to perform, even in the hands of those who do a great deal of surgical work. To recommend it as a procedure for the casual ophthalmic surgeon is not fair either to the patient or to the surgeon. Operation for any kind of glaucoma should be such that it can be performed by any surgeon in any part of the world and be foolproof against accident by the patient or the surgeon.

After operation, medical treatment must be continued, and usually is by all ophthalmic surgeons, until the intraocular tension is low enough to insure maintenance of vision and the visual fields. In experience, one finds hypotonia in many eyes after the Elliot operation or after iridencleisis, particularly after the former. Hypotonia generally causes loss of vision and loss of function of the eye. Of course, miotics should not be used in cases of hypotonia. The only cure for this condition is nature's method of filling in the drainage area, which has been made too large and is filtering too freely. If a surgeon could only estimate, even with a fair amount of accuracy, whether his surgical procedure would result in too much drainage or in too little! It is known, however, that a basal iridectomy never results in hypotonia.

#### CHRONIC SIMPLE GLAUCOMA

*Relation to Senility.*—This condition is a type of glaucoma associated with old age and is primarily due to sclerosis of the blood vessels and fibrosis of the tissues of the eyeball. I classify it as the dry form of glaucoma, in which the vascular injection plays a minor part. It is the glaucoma of the older portion of the old age group, between the ages of 60 and 80, and may be rightfully called the glaucoma of old age. It should not be compared with the wet types of glaucoma, in which the blood vessels undergo dilation and there is an acute or a subacute accumulation of fluids of variable degree in the interior of the eyeball.

In a survey of 1,876 cases of glaucoma at the Wills Hospital during the period from 1926 to 1935, inclusive, I found that chronic simple glaucoma constituted 73 per cent of all the cases of primary glaucoma, acute congestive glaucoma 11 per cent and chronic congestive glaucoma 16 per cent.

The type of glaucoma encountered most frequently in the practice of any ophthalmologist is that commonly called chronic simple glaucoma. It is not necessarily the end result of acute congestive or chronic congestive glaucoma, although in a few cases the congestive type may enter this stage if the patient lives long enough and the surgeon has not operated too hastily. Oftenest, however, chronic simple glaucoma is an entity in itself. It is merely the result of a pathologic change in the walls of the blood vessels, particularly in the region of the ciliary body, but associated with sclerosis of all the blood vessels of the eye, both

the anterior and the posterior segment. There is also fibrosis of the canal of Schlemm and of the spaces of Fontana, and the fibrosis of senility involves all cellular elements in the eye. While the congestive, or wet, types of glaucoma have as their mark of identification too much blood, the chronic simple type is characterized by an insufficient quantity of blood by reason of senile changes in the form of fibrosis, preventing the normal interchange of fluids which takes place in young tissue.

TABLE 2.—*Data on 47 Cases of Chronic Simple Glaucoma at Wills Hospital*

Vision*		5 to 10 Yr. (18 Cases)		2 to 5 Yr. (14 Cases)		2 Mo. to 2 Yr. (15 Cases)	
First	Final	Medical	Surgical	Medical	Surgical	Medical	Surgical
G	G	8	5	6	2	8	2
G	P	0	0	1	0	0	1
G	B	0	2	0	1	0	0
P	G	0	0	0	1	0	1
P	P	1	2	0	1	1	0
P	B	0	0	0	2	0	1
B	B	0	0	0	0	0	1

Interpretation: Good vision in eyes with chronic simple glaucoma is best maintained by medical treatment. Medical treatment, followed by surgical and then medical treatment, gives less satisfactory results.

\*G indicates vision of 20/100 or better; P, vision of 20/400 to 20/100 (partial blindness), and B, blindness, with vision of less than 20/400.

TABLE 3.—*Effect of Chronic Glaucoma on Vision of 47 Patients\**

	Blindness in Both Eyes		Partial Blindness in Both Eyes		Good Vision in One or Both Eyes	
	Medical	Surgical	Medical	Surgical	Medical	Surgical
5 to 10 yr.....	0	2	1	2	8	5
2 to 5 yr.....	0	3	1	1	6	3
2 mo. to 2 yr.....	0	2	1	1	8	3
Total.....	0	7	3	4	22	11

25 medical patients; 22 surgical (13 on whom Elliot operations were done elsewhere; 7 with blind eyes).

Interpretation: Total blindness occurs less frequently in medically treated eyes.

\*Blindness means blindness or vision under 20/400; partial blindness, vision of 20/400 to 20/100, and good vision, 20/100 or better.

*Treatment.*—The treatment for chronic simple glaucoma, therefore, is the treatment for senility. One must treat it kindly, gently, being conscious of the fact that senility is not a reversible process. True, in any stage of chronic simple glaucoma there may be occasional flare-ups resembling the wet types, because intermingled with senile cells there are always some cells which have retained the vitality to carry on. Usually, chronic simple glaucoma occurs in persons who do not have the cellular structure or the blood vascular system which can be provoked into an acute flare-up by the vasomotor and psychic stimuli to which younger tissues are subject.

I prefer medical treatment in all cases of chronic simple glaucoma for the duration of the patient's life even if the vision is not normal, the visual fields are cut down and the tension is not normal as compared with that of a young adult. I discourage surgical treatment for the

reduction of these symptoms, for most old people do not have normal vision or normal fields of vision and can get along very well with vision of much less than 100 per cent. It is only when the surgeon feels that the aged should have an intraocular tension equal to a fictitious normal and believes that the intraocular tension in an old person must equal a fixed normal on an artificial instrument that unnecessary surgical procedures are performed—not for the patient's "rainbows" but for the surgeon's, and a pot of gold!

The treatment I prefer is the use of miotics, principally pilocarpine nitrate, either a 0.5 or a 1 per cent solution, once daily, preferably at night, for the purpose of keeping the tension sufficiently low (or high) to give the patient freedom from symptoms. One should treat the patient with the idea of giving him comfort, rather than seek some artificial normal gage with an instrument which has neither feeling nor judgment.

I find that 70 per cent of all patients with chronic simple glaucoma can be made comfortable from the standpoint of visual function and mental happiness with medical treatment. When the intraocular pressure produces symptoms, I increase the strength of the miotic drug, either pilocarpine or physostigmine, or both, to bring about a reduction of symptoms sufficient only for relief. When I find that miotics are failing and the patient is losing his vision, then, and then only, do I resort to surgical measures.

#### ALLERGY TO SURGERY

The surgical operation must be simple and the technic such that any surgeon may be able to perform it with ease, and with as little damage as possible to the patient's eye. It must be borne in mind always that glaucomatous eyes of old people do not tolerate surgical procedures well. Despite statements by some surgeons that age in itself is not a contraindication to surgical intervention, it is my personal experience that extensive, meddlesome and fancy operations should not be performed on old persons with chronic simple glaucoma. The mental trauma resulting from any kind of operation on an old person is sufficient to undermine his morale and his physical resistance so as to interfere with healing. I have known old people who faded away physically under my care at the Wills Hospital merely because they had undergone a surgical ordeal. I therefore emphasize that surgical treatment of chronic simple glaucoma, especially in very old people, should be considered only as a last resort, and then only if the surgeon can give some degree of assurance that his surgical skill will benefit the patient. It is easy to try something on some one else's eye. A rough, trial and error surgical procedure should not be inflicted on any one, especially the aged. I have seen blindness resulting from surgical treatment, or at least provoked by it, in too many eyes

with chronic simple glaucoma.

When one has no alternative but to operate, the operation of choice for chronic simple glaucoma is iridencleisis. The second choice is my modification of the Herbert operation, in which a trapdoor is made in the region of the pars plana of the ciliary body. Such a trapdoor does little or no damage to the already diseased eye, and it enables the accumulated fluids to reach the outside slowly and continuously. The third operation, and the least desirable, is the Elliot trephination. I personally have seen too many tragedies resulting from the Elliot trephination in the hands of skilled and of unskilled surgeons. It is an operation which cannot be performed with skill by the average ophthalmologist. I prefer an iridecleisis or the Herbert operation.

There are other types of operations mentioned in the textbooks, and other types of medical treatment to which I have made no reference, but I omit them because in my experience I have found they have of little or no value.

Before operating in any case of chronic simple glaucoma the ophthalmologist should remember that old people prefer a little sight with glaucoma to a blind eye that apparently has been cured of glaucoma.

#### MEDICAL VERSUS SURGICAL TREATMENT

Bothman<sup>1</sup> stated:

Treatment of glaucoma is of two types, medical and surgical. Indications for surgery differ with the ophthalmologist. Some prefer to operate early, whereas others prefer to give miotics a fair trial first. The advocates of early operation put forth such arguments as (1) patients cannot be trusted to carry out treatment faithfully, (2) the patient may live a long distance from help in case of an acute attack, and (3) surgery eliminates use of drops (miotics). To some extent, they are correct, but every ophthalmologist has seen cases in which he later wished that surgery had been postponed. Complications and surgical accidents cannot always be avoided. With ignorant and uncooperative patients, medical treatment may be hazardous. However, we have seen a great many patients who faithfully carry out treatment for indefinite periods, 20 years or more.

Acute glaucomatous attacks do not require emergency operations; in fact, such an operation may be disastrous. Every effort must be made to reduce the tension to normal or to as low a level as possible before surgery is attempted. It is hardly conceivable that in the United States a patient with an acute attack could not get help within four to six hours [page 7].

The frequency with which trephine openings close or other types of operation fail to keep the tension within safe limits is familiar to everyone. Too large a percentage of patients require miotics postoperatively for one to be able truthfully to tell a patient that he will not need drops after surgery. The best that can be said is that he may not need them [page 8].

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1. Bothman, L., and others: 1945 Year Book of Eye, Ear, Nose and Throat, Chicago, The Year Book Publishers, Inc., 1946, pp. 7 and 8.



### Duke-Elder stated:

To give a prognosis of a composite entity such as primary glaucoma is impossible. On the whole, however, it may be said that, although exceptions do occur, without treatment the disease is progressive and results in absolute bilateral blindness. With adequate treatment the majority of simple compensated glaucomas can be stabilized or their progress delayed so that useful vision remains until the death of the patient; fortunately most patients are old, but a juvenile glaucoma is an unpleasant problem. Quite a number, however, particularly those of the sclerotic type, gradually and imperceptibly go down-hill even although the tension is adequately controlled; the deterioration is part, although it may be the most conspicuous part, of a general pathological process which is beyond medical control. Again in this, as in all other types of glaucoma, a malignant form occurs, which progresses, and frequently progresses rapidly, despite all treatment. In general terms it may be said in simple glaucoma that with reasonably adequate treatment some 70% of cases do well in so far as they become stabilized, 20% deteriorate so slowly that they retain a useful amount of sight to the end, while 10% do badly. In acute congestive glaucoma approximately the same figures can be obtained if the attack is overcome rapidly by medical treatment and a prophylactic operation is done on a quiet eye, but if the condition has lasted longer than 48 hours or if resort has been necessarily made to surgery of a more desperate type, the figures are considerably worse and a disappointing end-result in 30% is to be expected. In chronic congestive glaucoma, allowing for the great clinical variations between different cases, the figures lie between the former two [page 3414].

The local treatment to the eye is best considered separately for each clinical picture. It is to be remembered that *in every unilateral case the other eye should be held suspect* and every operation on one eye should be preceded by eserine in the other to eliminate the effect of axon reflexes between the two.

This last point is a matter of great importance. Any intra-ocular operation—apart altogether from glaucoma—is accompanied by a reflex hypo- or hypertensive reaction in the other (Towbin, Protopopow and Urishewaskaja,<sup>a</sup> 1934), and in an eye predisposed to glaucoma (as the fellow eye of a glaucomatous one frequently is even although it appears normal) this reflex reaction may be, and frequently has been, disastrous [page 3408].

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#### Wills Hospital.

2. Duke-Elder, W. S. : Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, pp. 3408 and 3414.

3. Towbin, B. G. : Protopopow, B. W., and Urishewaskaja, W. S. : Ueber die Wirkung des operativen Eingriffes in eines der beiden Augen auf den intraokularen Druck des anderen Auges, Arch. f. Ophth. **131**:554, 1934.

## RETROLENTAL FIBROPLASIA

### A Preliminary Report

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**O**PACIFICATION immediately behind the lens appearing in infants at or within a short time of birth, often associated with persistence of the hyaloid artery and its branches, or other abnormalities of the vitreous and the inner layer of the secondary optic vesicle, has long been described in the literature. The difference between these abnormalities and glioma, or malignant fungus, and congenital cataract was recognized by early writers in ophthalmology. Travers,<sup>1</sup> in 1820, described the case of a child of 8 months in which he extirpated the globe and observed the vitreous filled with an "opaque lardaceous substance, by which the lens was slightly protruded and the iris rendered convex. The retina for the most part was absorbed, and the other tunics perfect." He also observed a child from the age of 3 months who had a similar condition, while the pupil of the other eye was constricted and closed by an opaque capsule. Frick,<sup>2</sup> in 1826, described what was apparently this condition as congenital cataract, appearing several days or weeks after birth. Wecker,<sup>3</sup> in 1866, observed a case of persistent hyaloid artery coexisting with a luxated cataract and cited Meissner, in 1857, and Saemisch and Zehender, in 1863, as describing persistent hyaloid arteries in man. Nettleship,<sup>4</sup> in 1873; Gardiner,<sup>5</sup> in 1880; Holmes,<sup>6</sup> in 1881; Vassaux,<sup>7</sup> in

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Presented at the Alumni Meeting, Institute of Ophthalmology, of the Presbyterian Hospital, New York, May 1, 1948.

1. Travers, B.: *Diseases of the Eye*, London, Longman, Hurst, Reese, Orme and Brown, 1820, p. 203.

2. Frick, G.: *Diseases of the Eye*, London, John Anderson, 1826, p. 164.

3. Wecker, L.: *Maladies des yeux*, Paris, A. Delahaye, 1866, vol. 2, p. 300.

4. Nettleship, E.: *Curator's Report 187: Vascular Cord Traversing Vitreous and Co-Existing with Great Plastic Inflammation of Hyaloid*, *Ophth. Hosp. Rep. London* 7:632, 1781-1873.

5. Gardiner, E. J.: *A Case of Persistent Hyaloid Canal and Artery*, *Arch. Ophth.* 9:473, 1880.

6. Holmes, E. L.: *A Case of Persistent Hyaloid Canal*, *Arch. Ophth.* 10:168, 1881.

7. Vassaux, G.: *Persistence de l'artère hyaloïdienne et de la membrane pupillaire, ayant déterminé des altérations intra-oculaires, simulant cliniquement un néoplasme*, *Arch. d'opht.* 3:502, 1883.

1883, and numerous others later described this, or a similar, condition. Terry,<sup>8</sup> however, first called attention to the frequency of the condition in prematurely born infants and expressed the belief that the condition was different from that occurring in full-term infants. Reese and Payne<sup>9</sup> stated the belief that the same lesion may occur in both premature and full-term babies. Krause<sup>10</sup> described a large number of cases, in some of which the condition was associated with other defects of the central nervous system, particularly encephalic dysplasia. Cordes<sup>11</sup> has summed up the papers by these recent authors.

In studying the literature on this abnormality, and my own cases, comprising over 30, I came to the belief that the vascular fibrous tissue behind the lens was due to abnormal formation of the secondary and tertiary vitreous, causing an arrest of regression of the embryonic hyaloid vascular system, or at least a re-formation of this system, with revascularization of the abnormally dense vitreous structure. I concluded, also, that in certain instances there was vascularization of the already formed membrane from the peripheral retina, as evidenced by vessels radiating from the periphery to the center in the retrolental membrane, instead of from the center, as they usually did.

However, in observing the eyes of premature infants from birth, I rarely saw remnants of the hyaloid artery, and these disappeared shortly. None of these infants was born with a retrolental membrane. In 2 infants that I saw shortly after birth, nearly a year ago, without evidence of ocular abnormality, retrolental fibroplasia has since developed. I have therefore come to the conclusion that retrolental fibroplasia as it is usually known is not congenital, and is probably not related to uterine circumstances, except that of premature birth itself. The Owens<sup>12</sup> have also recently stated that retrolental fibroplasia is not derived from the hyaloid vascular system but is preceded by dilatation of the retinal vessels, especially the veins, appearing first at about the age of 85 days, followed by peripheral detachment of the retina, with formation of the retrolental membrane, which appears at approximately the age of 100 days. They

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8. Terry, T. L.: Extreme Prematurity and Fibroplastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens, *Am. J. Ophth.* 25:203, 1942.

9. Reese, A. B., and Payne, F.: Persistence and Hyperplasia of the Primary Vitreous, *Tr. Am. Ophth. Soc.* 43:163, 1945.

10. Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, *Arch. Ophth.* 36:387 (Oct.) 1946.

11. Cordes, F. C.: Types of Congenital Cataract, *Am. J. Ophth.* 30:397, 1947.

12. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia, read at the seventh clinical meeting of the Wilmer Residents' Association, Baltimore, April 14, 1948.

saw the membrane develop in 15 cases. In some of these cases there were yellowish retinal exudates, but no retinal hemorrhages.

In only 1 case have I seen what appeared to be so-called retrolental fibroplasia begin and watched its development to completion. In this case, that of an infant weighing 2 pounds 10 ounces (1,191 Gm.) at birth, the retinal vessels began to increase greatly in caliber and tortuosity in the fifth week of life. Numerous striate, superficial, roughly oval retinal hemorrhages appeared also at this time. Arteriovenous communications formed between the retinal artery and its accompanying vein in some places, usually at the midperiphery, and sometimes the hemorrhage surrounded the junction of vein and artery. Most of the hemorrhages, some of the arteriovenous communications and the tortuosity disappeared in a week or two. However, when the arteriovenous communication remained, the portion of the vessels comprising the U remained large, but the distal portion of the retinal vessels shrank. In the eighth week a pink haze developed just anterior to an arteriovenous junction in the lower portion of the fundus of each eye, which was due presumably to extravasated blood from the dilated, thin-walled vascular loop. These areas increased in size and projected forward into the vitreous. In the tenth week blood vessels could be seen in the nebulous preretinal masses. As the nebulae increased in size, they became more vascularized and migrated centrally, obscuring the central portion of the vessels of their origin and then the disk, and gradually occupying the area of Cloquet's canal. Slowly the nebulae changed in character, becoming completely vascularized, denser, quite clearly defined and smaller in diameter, to become centrally placed, irregular columns extending forward from the region of the disk toward the lens by the growth anteriorly of vascular loops. These loops projected forward like fimbria from various places in the mass, with practically no supporting tissue. However, at the time of writing, in the fourteenth week of life, the deeper portions of the mass are changing color, from dark gray to dense white. The mass has reached the lens in each eye, but there may be some regression, due perhaps to the repeated transfusions. A large preretinal hemorrhage surrounding the base, and possibly arising from the angioplastic column, has been present in the left eye since the tenth week of life. The rest of the vitreous, which became quite hazy with the appearance of the preretinal nebulae, cleared for a time, and small retinal vessels running to the periphery could be seen. However, the vascular tissue in the right eye has spread from just temporal of center over the whole posterior surface of the lens, while that in the left eye has not changed.

In twins, weighing 3 pounds 10 ounces (1,644 Gm.) and 3 pounds 9 ounces (1,716 Gm.), respectively, who continued to have prominent pupillary membrane loops, the retinal vessels became tortuous, with racemose aneurysms, in the fifth week also, and at the same time the pupillary vessels became engorged. In these infants, as well as in all others at the beginning of the appearance of abnormal processes, the pupils dilated poorly with cycloplegics and mydriatics. This phenomenon lasted two or three weeks, or longer. In 1 of the twins, however, retinal hemorrhages appeared in only one eye. The infants were discharged during their sixth week of life and were not seen again for a month. When again examined, they had the angiofibrous columns in the vitreous extending from the region of the disk, similar to those in the first case, and in all four eyes the mass touched the lens. In the left eye of 1 of the twins the angioplastic mass is loosely knit and spread out, so that the optic disk and the origin of the vitreous vessels can be seen well because of the lack of intervacular tissue. All the main vessels of the vitreous have the appearance of being pulled forward into the vitreal

mass in front of the disk practically from their origin, and send only small branches onto the surface of the retina. Apparently, all the retinal portions of these retinal vessels have shrunk, owing to the parasitic vitreous branches. A preretinal hemorrhage surrounds the column in the vitreous of the right eye of the other twin. The pupillary loops, although present, have become very small in these eyes.

It appears that this formation of vessels in the vitreous might be the hyaloid vascular system when it is quite fully formed. However, in the first case, at least, the mechanism of its formation was seen to be leakage of blood from the retinal vessels into the vitreous, followed by vascularization of the hemorrhage in the vitreous from the retinal vessels. The hyaloid artery, or its remnants, were not persistent in any of these cases, at least by the second week after birth, and certainly played no part in the formation of the angioplasia of the vitreous. I feel sure that this condition, in time at least, if untreated, will become a typical retrolental fibroplasia by spreading over the posterior surface of the lens and opacifying the mass by the further formation of intervascular fibrous tissue. This formation seems to be akin to the formation of granulation tissue elsewhere in the body, to retinitis proliferans or to the syndrome of von Hippel's angiomas.

In these 3 cases, as well as in many others, the peripheral portion of the fundus was pale gray from birth, the pallor persisting for several weeks at least. In certain cases this appears to be due to peripheral detachment or to failure of coaptation of the peripheral retina, for the retina is opaque, flat and elevated, with retinal vessels running over it. However, in some cases this peripheral pallor seems to be due, at least in part, to a peripheral haze in the vitreous or to failure of the vitreous to clear peripherally, which may be the effect of a structural abnormality of the secondary vitreous there. The retinal vessels, when dilated in the 3 cases described, were dilated as far peripherally as could be followed, but they are, of course, attenuated now; the peripheral retina, however, is still pale, and perhaps elevated.

In another infant, weighing 2 pounds 4 ounces (1,020 Gm.) at birth, the retinal vessels remained consistently small, but the peripheral vitreous is still very hazy and the peripheral retina elevated, although it cannot be seen well. In the sixth week of life many small, striate retinal hemorrhages appeared, but disappeared by the next week. At the time of this report, in the tenth week, in certain portions of the fundus the central edge of a thin membrane can be seen lying close behind the periphery of the lens, and in the frontal plane of the eye. It is not vascular and appears to be due to a condensation of the peripheral portion of the vitreous. In 1 eye there is also a dark brownish red, sheetlike mass without visible vessels, of triangular shape, one point of which is in the mid-vitreous, not far back of the lens. Another point joins the peripheral membrane, and the third point attaches at the disk and is in contact with the retina for at least a portion of the way to the periphery, where it is lined with pigment along the sides, like a typical retinal fold. The vitreous has been so hazy during the development of the tissue last described that I cannot tell how it originated, but early in life the disk and the posterior portion of the fundus were clearly seen.

Blackfan and his associates<sup>13</sup> stated that in the premature infant during the first three months of life there are a rapid decrease in the number of red blood cells, and an even more rapid diminution in hemoglobin. This change is thought to be due to the same mechanism as that which influences the development of physiologic anemia in full-term infants. The premature infant grows at a relatively faster rate than the full-term infant; consequently, there are a greater demand for blood and a less actively functioning hemopoietic system. The anemia is characteristic of all premature children. The severity is proportional to the state of prematurity. In premature infants weighing 5 pounds (2,268 Gm.) or more at birth, the number of red blood cells and the hemoglobin concentration are not altered as much as in those weighing less. Severe anemia begins in the second week and continues to become severer until the eleventh or twelfth week, when the erythrocytes begin to increase steadily in number, until by the seventh month the values are those for full-term children of the same age.

There have been very low hemoglobin values and red blood cell counts in all the cases described, but we did not begin to make the blood studies early or frequently enough to permit the establishment as yet of a definite correlation between the pathologic process described and the anemia. There may be a correlation between transfusion of citrated blood and arrest, and perhaps regression, of the pathologic process in some cases, especially notable in shrinking of the new-formed vitreous vessels, retraction of the vitreous membranes and clearing of the peripheral vitreous.

Although at present unproved, it appears that the anemia of prematurity in itself may be a factor at least in the causation of retrolental fibroplasia. I do not mean that low hemoglobin and red blood cells alone are necessarily of significance; rather, a low or high concentration of some other, as yet unknown, substance in the blood may have a part in the anemia. The secondary vitreous, because of this anemia, may change in character or fail to develop normally, or may contain some substance which is irritating to the retinal vessels and stimulates formation of new vessels from the retina. At any rate, except for undoubted cases of embryonic arrest, I feel that it can be stated that so-called retrolental fibroplasia in premature infants is not congenital and is not due to persistence of the embryonic vascular structure, but that it is a postnatal pathologic condition in which the retinal vessels play a prominent role, but which appears to be stimulated by some abnormality of the vitreous.

This concept of the formation of retrolental fibroplasia, with secondary contractures and changes, would explain the pathologic picture in

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13. Blackfan, K. D.; Diamond, L. K., and Leister, C. M.: *Atlas of the Blood in Children*, New York, The Commonwealth Fund, 1944.

the cases of the fully developed abnormality I have observed, as well as those described in the literature. There appear to be two main types of the condition. The first develops from the proliferation of vascular tissue from the retinal vessels of the posterior portion of the fundus into abnormal vitreous, probably usually with hemorrhage. The second is the result of failure of development or condensation of the secondary vitreous at the anterior periphery, with proliferation into it of retinal vessels from the unattached peripheral portion of the retina. There may be combinations of the two types. A similar intracranial pathologic process might well explain Krause's "encephalo-ophthalmic dysplasia." The occurrence of dilated retinal and pupillary vessels, the difficulty in dilating the pupils, the frequent finding of posterior synechias later, the anterior peripheral and preapillary haze in the vitreous and the failure of normal enlargement of the globes in some cases seem to point to postnatal iridocyclitis and hyalitis as the basic pathologic process. The etiologic factor is at present obscure, but may well be a physicochemical pathologic process, affecting principally the ciliary body at a crucial period of development and the secretion of secondary and tertiary vitreous.

This paper is not a full report of the study, which will be completed later; rather, it is intended merely to be provocative of investigation by other workers, in the hope that this devastating process in infants may be prevented.

179 Allyn Street.

# Clinical Notes

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## A SIMPLE APPOSITIONAL SUTURE FOR USE IN OPERATIONS FOR CATARACT

CHARLES A. PERERA, M.D.  
NEW YORK

The effect of corneoscleral sutures in reducing the complications following operations for cataract has been demonstrated by many competent ophthalmic surgeons. These sutures may be classified into four main types: (1) sutures placed before the eyeball has been opened; (2) sutures anchored before the globe has been incised, and completed after the incision; (3) sutures placed after a keratome incision or after a short incision made with the Graefe knife, before the opening has been enlarged, and (4) sutures placed after the incision has been completed.

The ideal corneoscleral sutures are those which exactly approximate the wound edges, i.e., appositional sutures. Appositional sutures placed before the operative incision into the eyeball have been described by Verhoeff<sup>1</sup> and by McLean.<sup>2</sup> The latter author, after reviewing the literature, reported a modification of the suture originally described by Suarez de Mendoza in 1892 and reintroduced with variations by Lindner in 1938.

The trauma of inserting corneoscleral sutures may add to the risk of operation for cataract, especially in an eye containing a subluxated lens or a fragile zonular membrane. This trauma is negligible if the sutures are placed before the globe is opened, and minimal if the sutures are inserted when the incision into the anterior chamber is small and incapable of gaping.

There is an increasing tendency among ophthalmologists to make use of the keratome in performing operations for cataract, and then to enlarge the wound with scissors. Appositional sutures can be easily introduced after a keratome incision, as described here.

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Read at the Eighty-Fourth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., May 17, 1948.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology of Presbyterian Hospital.

1. Verhoeff, F. H.: A Corneo-Sclero-Conjunctival Suture in Operations for Cataract, *Tr. Am. Ophth. Soc.* **25**:48-53, 1927.

2. McLean, J. M.: A New Corneoscleral Suture, *Arch. Ophth.* **23**:554-559 (March) 1940.



TECHNIC OF PLACING APPOSITIONAL SUTURES  
AFTER KERATOME INCISION

After the usual preoperative preparation of the patient, including akinesia, retrobulbar injection of procaine and placement of a traction suture through the superior rectus muscle, the lids are held apart by a

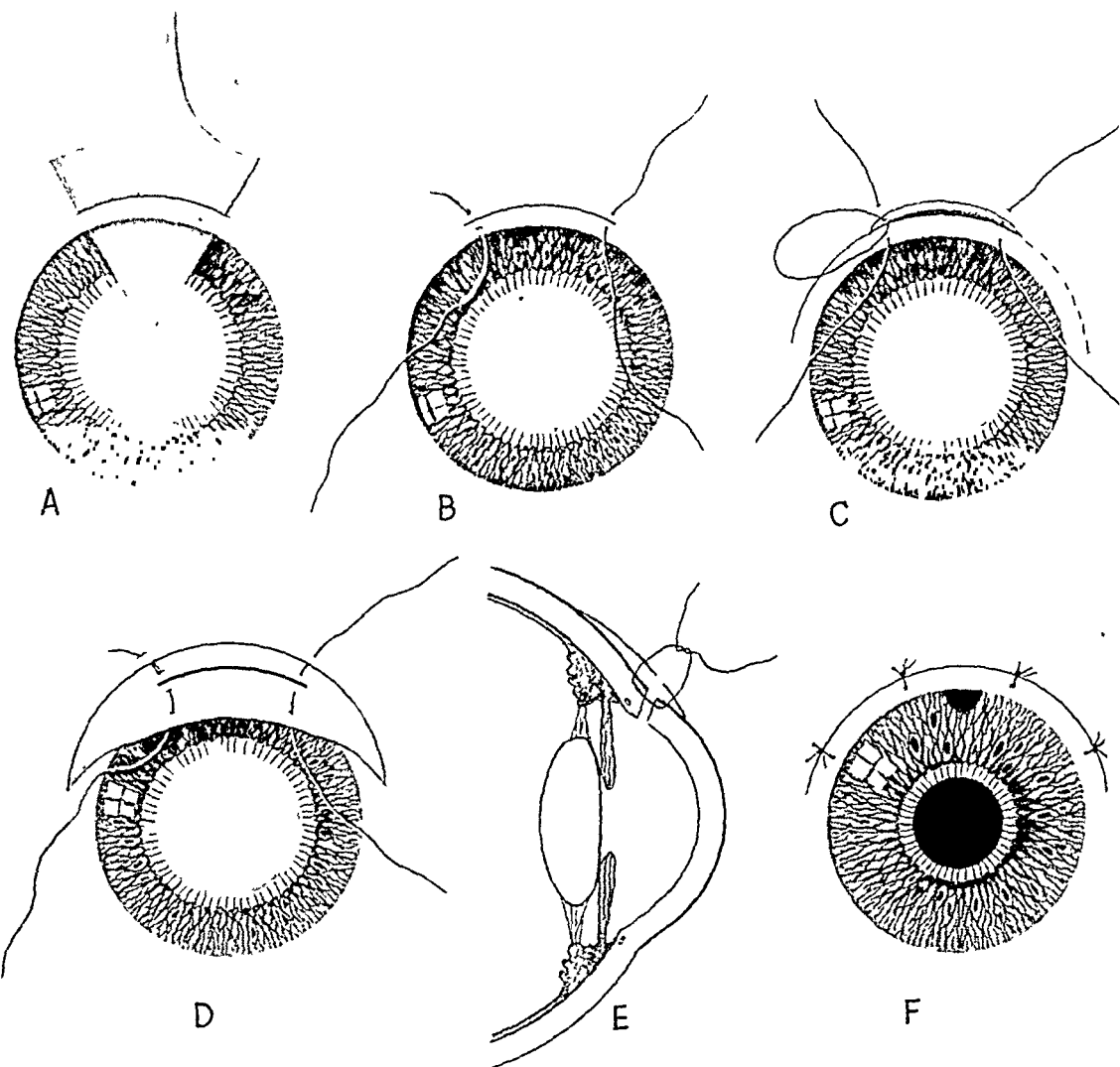
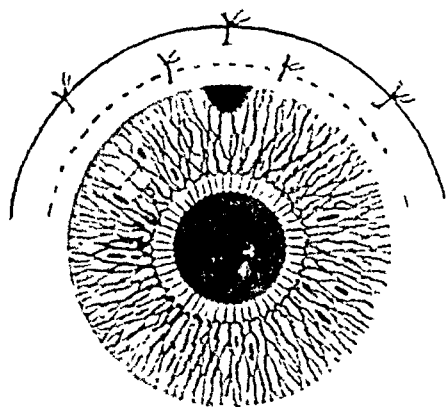


Fig. 1.—*A*, *B* and *C*, appositional sutures placed after keratome incision. The conjunctiva is not shown. *A*, limbal keratome incision; *B*, sutures passed through extremities of wound; *C*, suture looped out and incision completed.

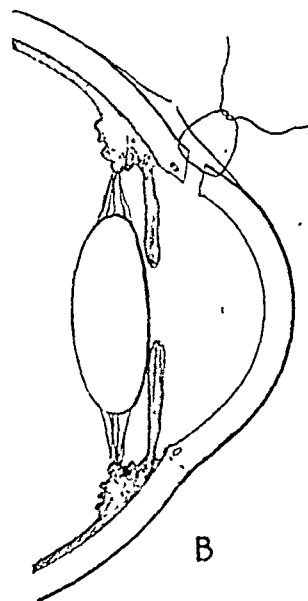
*D*, *E* and *F*, appositional sutures with narrow conjunctival flap. *D*, sutures placed after 2 mm. conjunctival flap has been turned down over cornea; *E*, cross section of eyeball, showing one suture; *F*, appearance after completion of operation. The conjunctiva is closed with two additional sutures.

speculum, special clamps or lid sutures. A limbal keratome incision is made superiorly with or, if this is contraindicated, without a conjunctival flap. The limbal incision may be made with a Graefe or a Wheeler knife, and it may be placed in any quadrant desired. At this point, a

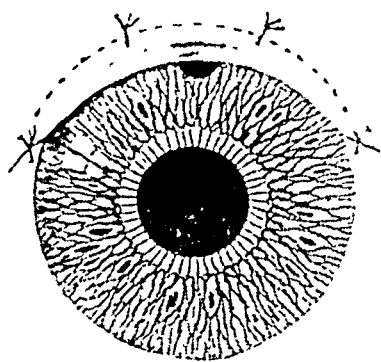
fine silk suture is passed through the anterior margins of the corneoscleral wound close to each extremity of the keratome or knife incision. If a conjunctival flap has been fashioned, the sutures are also passed through the conjunctival margins or in mattress style through the flap. These sutures are placed so close to the extremities of the wound that they bite into apposed portions of the wound edges. Fixation for this maneuver is obtained by applying scleral fixation forceps posterior to



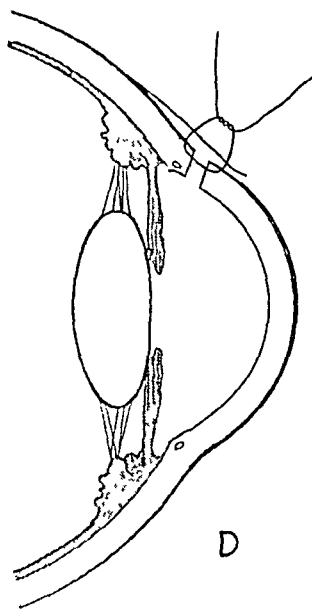
A



B



C



D

Fig. 2.—*A* and *B*, appositional sutures with large conjunctival flap. *A*, appearance at close of operation, showing corneoscleral sutures tied in mattress fashion through conjunctival flap. Conjunctival margins are approximated with three additional sutures. *B*, cross section through a corneoscleral suture.

*C* and *D*, appositional sutures with sliding conjunctival flap. *C*, appearance at completion of operation, showing corneoscleral sutures tied through conjunctival flap. Two laterally placed conjunctivoepiscleral sutures hold conjunctival flap in place. *D*, cross section through a corneoscleral suture.

the site of the suture, or by grasping a margin or the extremity of the wound with fine conjunctival forceps. Then the sutures are looped out of the incision, which is completed with scissors. At the close of the operation, additional sutures may be inserted into the conjunctival flap if indicated.

I have used these sutures for over ten years, with satisfactory results. This method of suturing has been employed by some of the resident ophthalmologists on the service of Dr. A. B. Reese at the Institute of Ophthalmology of Presbyterian Hospital.

One case of postoperative prolapse of the iris occurred in the last 100 cataract operations in which I made use of these appositional sutures. This series include 80 intracapsular extractions of the lens, among which were 6 loop extractions of dislocated lenses and 9 instances in which the lens capsule was opened accidentally or intentionally to permit grasp of a taut lens capsule. A complete iridectomy was performed in 46 cases, in 5 of these before the the cataract operation.

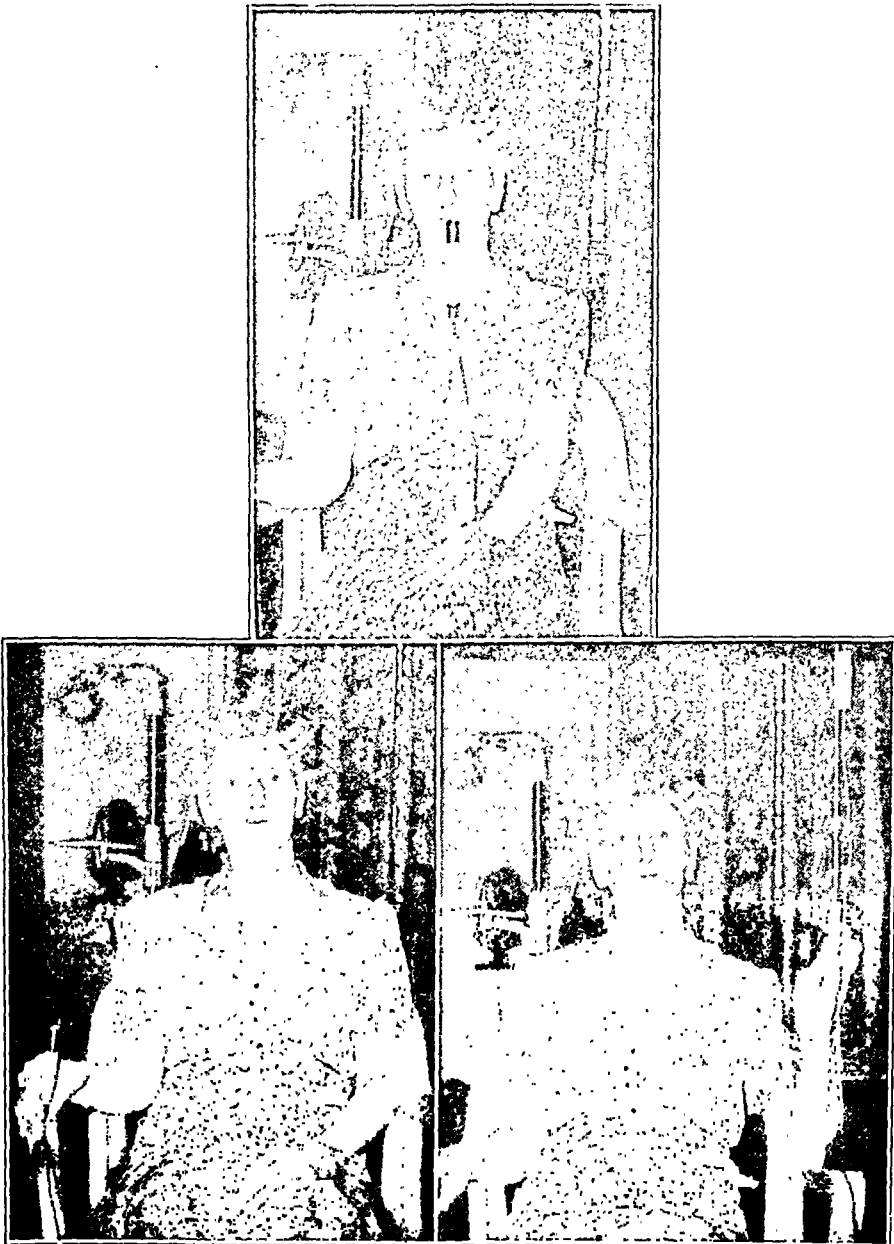
The instance of prolapse of the iris occurred in a man 81 years of age. The appositional sutures were placed as shown in figure 2*A* and *B*. A peripheral iridectomy was performed at the 12 o'clock position. The lens capsule tore at the site of application of the Arruga forceps below the lower border of the pupillary area, but the instrument was reapplied to encompass the tear and the lens was removed in its capsule. The patient got out of bed during the night following the operation. At the first dressing, three days after operation, the anterior chamber was filled with blood, which extended beneath the conjunctival flap. When the blood was absorbed, a small prolapse of the iris was seen on the lateral side of the temporal corneoscleral suture, beneath the conjunctival flap.

70 East Sixty-Sixth Street.

## FIXATION LIGHT

JOHN V. McMACKIN, M.D.  
MIAMI, FLA.

The screen test is being used oftener in examination of ocular motility than formerly. As a result, more apparatus is being devised for the technic. Some time ago I devised what I believe is the simplest, although perhaps not the most accurate, device to use in certain cases in which more elaborate apparatus cannot be used, especially in handling children and when one has no assistant or nurse to hold a target. The child now helps in the game to be played.



The apparatus consists of a metal wire fly swatter, with the swatter part sawed off; a National bulb holder and bulb attached to the end with adhesive tape, and cord running to the volt controller. This gives a handle 18 inches (45 cm.) long, with the bulb on the upper end.

With the patient seated in an ordinary arm chair, all the cardinal positions of gaze can be measured, the examiner watching only the central portion of the head, which he is watching anyway. After a little practice the examiner can have the light target in any position desired, with extreme comfort to the patient and plenty of space for the physician to make the screen test.

When the lower fields are to be examined, the patient holds the bulb holder at the arm of the chair.

406 Huntington Building (32).

## Abstracts From Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

### Anatomy and Embryology

THE TROCHLEAR NERVE IN THE HUMAN EMBRYO AND FOETUS. E. R. A. COOPER, Brit. J. Ophth. **31**:257 (May) 1947.

The trochlear complex as seen in a series of human embryos and fetuses (4 mm. onward) is described. An account of the development of the isthmus rhombencephali is also included. The question how the trochlear nerve reaches the dorsal region of the brain stem is answered, and the nature of the decussation is described. The investigation has not revealed why the decussation occurs or why it takes place on the dorsal aspect of the brain stem. The trochlear nucleus originates in series with the oculomotor nucleus, but in the basal plate of the isthmus. As the lateral walls of the isthmus link the metencephalic alar to the mesencephalic basal plate, the basal plate of the isthmus becomes compressed until it assumes a position at the ventral extremity of the lateral wall of the isthmus, and it is here that the trochlear nucleus is situated at first. The fibers from the nucleus form a bundle, which turns dorsally at once and thus gains an alar situation in the lateral wall of the isthmus. The nerve then proceeds through the lateral wall of the isthmus caudally to the superior medullary velum, where the decussation occurs. The article is illustrated with unusually fine photographs.

W. ZENTMAYER.

### Conjunctiva

OPERATIVE TECHNIC FOR POSTERIOR SYMBLEPHARON. E. ROMERO, Arch. Soc. oftal. hispano-am. **6**:1161 (Nov.) 1946.

The author, aware that recurrence after the present operative procedures for posterior symblepharon is common, used a simple method of his own in dealing with this condition in 3 cases. With this procedure, a posterior symblepharon is changed into an anterior one by passing through the posterior part of the adhesion a thick needle threaded with a bundle of threads, which are left loose like a drain. A few days later, after epitheliation of the tunnel has taken place, the remaining bridge of tissue is cut as though one were dealing with an anterior symblepharon. Good results were obtained in the 3 cases in which the method was used.

H. F. CARRASQUILLO.

SPONTANEOUS PROFUSE HEMORRHAGE FROM THE CONJUNCTIVA OF BOTH EYES IN AN INFANT TREATED WITH BLOOD TRANSFUSION. I. SANDUKOVSKY and Z. DEGGELLER, Vestnik oftal. **25**:35, 1946.

A hemorrhage from the conjunctiva of both eyes was present in an infant on the second day after birth. The lids were edematous, and there

was continuous bleeding with formation of clots of blood in the conjunctival sacs. The blood picture was that of anemia: 65 per cent hemoglobin, 3,290,000 red blood cells and poikilocytosis. A history of hemophilia could not be established.

A transfusion of 50 cc. of blood was given on the following day; the bleeding stopped in a few hours and did not recur.

OLGA SITCHEVSKA.

### Cornea and Sclera

SCLERAL NECROSIS IN PERIARTERITIS NODOSA, F. HARBERT and S. D. McPHERSON JR., *Am. J. Ophth.* **30**:727 (June) 1947.

Acute otitis media developed in a 31 year old man, as well as abscess of the nasal septum and apparently an allergic reaction to sulfonamide compounds. He recovered, with considerable saddleback deformity of the nose, dacryocystitis and deafness. Following dacryocystectomy, bilateral superficial punctate keratitis occurred. A subconjunctival hemorrhage developed in each eye above the upper limbus. The conjunctiva became edematous and ulcerated. The underlying sclera sloughed and the interior of the eyes became involved, and final vision was 1/200 in the right eye and 2/200 in the left eye. Sections from the gastrocnemius muscle showed changes consistent with periarteritis nodosa.

W. S. REESE.

SURGICAL TECHNIQUE OF CORNEAL TRANSPLANTATION IN RABBITS. F. C. STANSBURY and J. A. C. WADSWORTH, *Am. J. Ophth.* **30**:968 (Aug.) 1947.

Stansbury and Wadsworth described a satisfactory method of keratoplasty on rabbits following in general the technic of Castroviejo. They recount the difficulties and methods of solving them.

W. S. REESE.

ACTINIC KERATOCONJUNCTIVITIS. V. CHULIA, *Arch. Soc. oftal. hispano-am.* **6**:1253 (Dec.) 1946.

The author concludes that there is no doubt of the importance of the physical constitution of the individual patient in the causation of actinic keratoconjunctivitis. He has never seen the condition in robust people with dark skin. Lymphatism in all its aspects (pale, thin skin; sparse pigmentation; weakness; underweight) are etiologic factors of importance. The sun, by the action of its rays, gives rise to the disease, but the aforementioned constitutional factors must be present for its occurrence.

H. F. CARRASQUILLO.

### Experimental Pathology

PRIMARY AND SECONDARY CHANGES IN THE EYE IN TULAREMIA. A. KRUTOVA, *Vestnik oftal.* **26**:23, 1946.

Krutova infected guinea pigs with tularemia by instilling 1 drop of pure culture of *Bacillus tularensis* into the conjunctival sac, or by inject-

ing the culture subconjunctivally; the other eye served as a control. Clinical changes similar to those in the human eye were observed on the fifth day of the experiment. The guinea pigs had a generalized infection and died on the third to the tenth day. The eyeballs, lids, internal organs and lymph nodes were examined under the microscope. The internal organs showed necrotic granulomatous foci. The conjunctiva showed necrosis and inflammatory infiltration. Specific granulomas were also found in the ciliary muscles, which was rather unusual. The control eye showed no changes.

The regional lymph nodes were not affected, as the guinea pigs died too soon from generalized infection; i.e., Parinaud's syndrome was absent.

Krutova described another infected guinea pig with generalized tularemia, in which secondary changes were observed in both eyes. There was no regional lymphadenitis. Episcleral necrosis appeared only on the eighth or ninth day.

Cutaneous changes of the lids and of the body were of the characteristic "rosette" form, similar to changes in the conjunctiva. These rosette changes in the skin, which appear on the eighth to the ninth day, and which may be called skin "granulomatosis," are secondary changes and are of hematogenous origin, or of the same origin as the secondary changes in the eye. The temperature flared up with the appearance of the cutaneous and ocular lesions.

Krutova believes that in a case of tularemia all organs should be carefully examined, as the spread of the disease might be extensive despite few subjective symptoms.

OLGA SITCHEVSKA.

### General Diseases

#### THE NEW OCULOBUCCAL-GENITAL SYNDROME: REPORT OF A CASE WITH VERIFICATION OF ACID-FAST BACILLI AND PATHOLOGIC EXAMINATION.

R. JEBEJIAN and B. KALFAYAN, *Ann. d'ocul.* **178**:335 (Aug.) 1945.

The authors report a case of the oculobuccal-genital syndrome which they have followed for nearly six years. The lesions are manifest chiefly on the mucous surfaces of the mouth, pharynx and genitals and in the eyes. The disease affects both sexes, and in the reported cases it has usually occurred in the second or the third decade of life. The three cardinal features may be present at the same time, or they may occur singly. The buccal lesions are most frequently aphthous ulcers. They are discrete and painful and disappear in a few days.

The genital lesions are also ulcerative. They occur on the scrotum or the vulvae. They may be single or multiple. They are painful and last anywhere from a few days to two weeks. The ocular lesion is most commonly a bilateral iritis, which is frequently accompanied with a hypopyon. Conjunctivitis, keratitis, uveitis, retinitis, neuroretinitis and optic neuritis may also occur.

The authors report the clinical course of their patient in detail. They describe the pathologic changes observed in one of the buccal ulcers which they excised. The most significant observation was the presence of an acid-fast bacillus, resembling the bacillus of avian tuberculosis. A general discussion of the reported cases is also presented. Adamentiades,



who reported the first case of this syndrome, expressed the belief that a staphylococcus was responsible for the lesions. Behcet, at a later date, suggested that the etiologic agent was probably a virus. Others have expressed the belief that the lesions are allergic. The authors hope to continue their investigations in other cases in order to verify their observation of an acid-fast bacillus.

P. ROBB McDONALD.

PHOTOPHOBIA ASSOCIATED WITH INFANTILE ACRODYNIA. I. ESENTE, Riv. di oftal. 1:392, 1946.

The author describes 5 cases of infantile acrodynia accompanied with photophobia. He presents a critical review of the more modern views on the pathogenesis and therapy of acrodynia and expresses favor toward the idea of a neurotropic factor or agent residing perhaps in the vegetative centers of the infundibulum and the tuber cinereum.

A contributing factor may be an avitaminosis, for relief of which various investigators prefer polyvitamin therapy, rich in the B factors.

The explanation of the photophobia on the basis of ocular hyperesthesia or a sympathetic state does not seem persuasive or adequate. The author feels that its origin lies either in a retinal hyperexcitability resulting from an altered local metabolism, and determined by the pathogenic agent operative in acrodynia, or in the absence of definite anatomic-physiologic connections between the diencephalon and the retina. He further believes that profound psychosomatic changes present in acrodynia by virtue of the disturbance in the higher vegetative centers may be responsible for the irritative state of the light sense, thus producing photophobia.

G. B. BIETTI—J. J. LO-PRESTI.

CEREBRAL COMPLICATIONS (PAPILLEDEMA) IN EPIDEMIC PAROTITIS. H. O. ESBJERG, Acta ophth. 21:119, 1944.

Two cases of papilledema as a sequel to epidemic parotitis are reported. The intracranial symptoms simulated those of a tumor in the roof of the fourth ventricle and are due to obstruction of the basal foramina caused by arachnoiditis.

O. P. PERKINS.

REITER'S DISEASE. M. ZEWI, Acta ophth. 25:47, 1947.

The author gives brief histories of 10 cases that seem to correspond to the description of Reiter's disease. Seven of the 10 patients showed the characteristic triad of polyarthritides, conjunctivitis and urinary tract disturbance. Three patients showed only the joint and eye symptoms. The author can shed no light on the pathogenesis of this queer condition except to stress that it seems to be in some way associated with an intestinal infection.

O. P. PERKINS.

## **Glaucoma**

THE USE OF FURMETHIDE IN COMPARISON WITH PILOCARPINE AND ESERINE FOR THE TREATMENT OF GLAUCOMA. E. U. OWENS and A. C. WOODS, *Am. J. Ophth.* **30**:995 (Aug.) 1947.

Owens and Woods conclude that "furmethide" (furfuryl trimethylammonium iodide) is more effective than pilocarpine and physostigmine in the treatment of primary glaucoma in which the tension exceeds 40 mm. of mercury (Schiötz). It is also effective in certain cases of primary glaucoma in the lower tension groups in which treatment with pilocarpine has failed.

W. S. REESE.

ROLE OF HEREDITY IN GLAUCOMA. S. A. FIALHO, *Rev. brasil de oftal.* **5**:19 (Sept.) 1946.

Clinical observations show that heredity plays an important part in the genesis of glaucoma. Von Graefe called attention to the "rule of anticipation" which is observed in familial glaucoma, the disease appearing earlier in successive generations. Numerous authors have confirmed this observation. Attention has also been drawn to the frequent appearance of glaucoma, with other hereditary anomalies, such as retinitis pigmentosa and aniridia. Special mention is also made of the fact that hereditary glaucoma is often associated with myopia, statistics having shown that 50 per cent of the cases of juvenile glaucoma occur in myopic persons. Racial influence has also been admitted, the Jews and Negroes being particularly disposed to the disease. The author presents 2 interesting cases, in 1 of which the disease was transmitted from the father to 2 of his 6 children. In the other the disease has appeared in three successive generations and is manifest in the fourth. Both case histories confirm the "rule of anticipation."

M. E. ALVARO.

PERIPUPILLARY WEB OF VESSELS IN HEMORRHAGIC GLAUCOMA. E. HOLM, *Acta ophth.* **23**:343, 1945.

Ten cases are described. The author stresses peripupillary infection as an important diagnostic sign of hemorrhagic glaucoma. The vascularization consists of loops of vessels, forming a layer anterior to the pupillary sphincter. That such new-formed vessels occur in cases of old hemorrhagic glaucoma has long been known, but the author holds that they are present immediately after symptoms of glaucoma develop. Subsequently, the picture is altered by the ingrowth of vessels from the periphery of the iris.

Thiel thinks the vessels form in consequence of stasis due to increased tension.

The author regards arteriosclerotic lesions of the vessels, with obstruction of many uveal vessels, as a reasonable cause.

O. P. PERKINS.

## Lacrimal Apparatus

CONTRIBUTION TO THE STUDY OF CONGENITAL FISTULA OF THE LACRIMAL SAC. M. TORTI, Ital. d'ottal. 13:69, 1946.

After a brief review of the bibliography, the author reports 2 cases of congenital unilateral fistula of the lacrimal sac. From the histologic examination of the first case, in which numerous lymphocytes interspersed with mast cells and plasma cells were noted in the subepithelial connective tissue, an inflammatory origin was surely operative, while in the second case one was dealing with a congenital anomaly. According to the author, without a suitable histologic examination of sections of the tissues, one cannot make a diagnosis of congenital fistula even when the history dates back to earliest childhood and lacks inflammatory episodes. True congenital fistulas arise from the promotion of a supernumerary and aberrant lacrimal canal, developing in manner and time as do the normal lacrimal conalculi.

G. B. BIETTI—J. J. LO-PRESTI.

MASSIVE POLYP OF THE LACRIMAL SAC CURED WITHOUT INTERVENTION. F. A. CHAVARRIA LOPEZ, Arch. Soc. oftal. hispano-am. 6:1127 (Nov.) 1946.

The author differentiates between pseudopolyps occurring in a lacrimal sac the seat of a chronic inflammatory condition, which are merely sessile proliferations of the diseased mucous membrane, and true polyps, which are pedunculated growths with a definite histologic structure.

The case of a man aged 24 who had previously had acute dacryocystitis in both eyes at different times is reported. Later acute inflammation of the right lacrimal sac again developed. An abscess was formed, which opened spontaneously. Through the aperture a large, pedunculated true polyp herniated. The patient himself ruptured the polyp while applying compresses which had been prescribed.

H. F. CARRASQUILLO.

## Lids

THE TREATMENT OF EPITHELIOMAS OF THE LIDS WITH RADIATION. (RADIUM AND ROENTGEN RAYS. MARC-ADRIEN DOLLFUS, Curie Foundation, 1946.

This 121 page supplement, read at the November 1946 session, must be perused in its entirety to realize the detailed study involved in this monumental work. The study began eight years ago in an effort to compare the surgical or diathermy coagulation approach with that of irradiation.

L. L. MAYER.

## Neurology

DIVERGENCE EXCESS: AN ANOMALY OF THE EXTRAPYRAMIDAL SYSTEM. E. HEALY, Am. J. Ophth. 30:753 (June) 1947.

Healy concludes that divergence excess is not correlated with refraction and that orthoptics is the most satisfactory treatment because it

corrects, to a great extent, the neurologic factor. He also concludes that divergence excess is an anomaly of the extrapyramidal system and that research in this field is urgently needed.

W. S. REESE.

MESENCEPHALIC PARINAUD'S PARALYSIS. J. VERDAGUER and M. L. OLIVERAS, *Arch. chilena de oftal.* 2:226 (July-Oct.) 1946.

A man 33 years of age with a syphilitic history, complaining of almost constant occipital headache and vertigo, presented the following ocular symptoms: visual acuity was 5/10 in the right eye and 5/7.5 in the left eye. The pupils were normal; the photomotor reflex, however, was abolished, but the reaction in convergence and accommodation was preserved. The fundus was normal in both eyes. Moderate exotropia was present in the left eye.

In performing the voluntary ocular movements there was marked limitation of the upward excursions, and in an effort to turn the eyes straight up the upper lids were retracted and convergent and divergent movements were initiated, those of divergence predominating. On looking up and to the right and up and to the left, the eye in adduction moved to a higher level.

The reflex upward movements were also restricted, and Bell's phenomenon was absent. There was diplopia in looking up and to the right and up and to the left.

The visual fields showed slight bitemporal limitations and enlargement of both blindspots. Results of the clinical laboratory examination were essentially negative, except for an increase (4 Gm.) in the albumin content of the cerebrospinal fluid.

Roentengrams were suggestive of a cerebral tumor in the quadrigeminal region, showing destruction of the posterior clinoid processes and the dorsum sellae.

The authors make a complete analysis of the case, and since the patient showed partial paralysis of the associated movements of elevation and the automatic reflex movements (incomplete paralysis of convergence and Argyll Robertson pupils) he arrived at the diagnosis of Parinaud's syndrome. As to the etiology of the condition, he believes the causative factor to be an intracranial tumor located in the quadrigeminal region; this impression is sustained by the roentgenograms and the increased albumin content of the cerebrospinal fluid.

H. F. CARRASQUILLO.

### Ocular Muscles

DIVERGENT AND CONCOMITANT STRABISMUS. R. ARGANARAZ, *Arch. de oftal. de Buenos Aires* 21:67 (April-June) 1946.

Argañaraz classifies strabismus as follows: 1. Divergent functional strabismus, usually noted at the end of the first period of infancy, although it may not appear until between the ages of 6 and 12 years. The stimulus to divergence, although weak, is permanent and thus tends to increase. This class of strabismus is difficult to treat surgically with success, as it is necessary to overcome the dynamic spasmodic action of

five of the six extraocular muscles. 2. Divergent strabismus due to amblyopia. When one eye ceases to function as a result of amblyopia, the retinal stimulus which keeps the eyes parallel is gradually lessened and the weak eye deviates outward for approximately 23 degrees. 3. Postoperative divergent strabismus. This type usually appears some time after tenotomy of the medial rectus muscle. It is noted in cases in which an extensive capsular débridement was carried out with the tenotomy or when the section of the medial rectus muscle was made 5 mm. or more from its scleral insertion. 4. Spasmodic divergent strabismus caused by the spasmodic contraction of the inferior oblique muscle, which rotates the eye outward and elevates the eyeball. The patient's head inclines toward the unaffected side; the head is carried forward until the chin touches the chest and is turned inward to compensate for the divergence. In the other eye the symptoms are exactly the reverse, owing to hypofunction of the superior rectus muscle. Tenotomy of the inferior oblique muscle is the only surgical procedure in cases of this type. 5. Paralytic strabismus (convergent and divergent). In a child, isolated paralysis of the medial rectus muscle is rare and when present causes a deviation of the eye outward. Paralysis of the lateral rectus muscle is much commoner and causes a strong convergent strabismus. These squints are easily recognizable, and they are noticeable from birth, the deviation often reaching 40 to 45 degrees. The author recommends tenotomy of the medial rectus muscle in cases of this type. Advancement and shortening of the lateral rectus muscles may also be performed. In cases of convergent strabismus controlled tenotomy and retroinsertion are recommended. Myectomy of the medial rectus muscle can also be associated with tenotomy of the lateral rectus. Surgical correction of postoperative divergent strabismus is difficult, and a muscle transplant is necessary. Tenotomy of the inferior oblique at its insertion on the lower orbital border is recommended in treatment of divergent strabismus in infants. A muscle transplant is the procedure of choice in treatment of paralytic strabismus, in order to replace the action of the paralyzed muscles. The article is accompanied with 20 illustrations.

M. E. ALVARO.

## Operations

PRESENT EVALUATION OF THE MERITS OF THE Z-PLASTIC OPERATION.  
JOHN S. DAVIS, *Plastic & Reconstruct. Surg.* 1:26 (July) 1946.

Denonvilliers is credited with creating the Z plastic operation in 1856. He made an incision shaped like a Z and transposed the two triangular flaps, obtaining relaxation and extension of tissue to correct ectropion. Morestin was the first to use multiple Z incisions in series. The mathematical basis worked out by Limberg gave the surgeon accurate information on how long the arms of the Z should be and on the best size of the angles formed by these arms.

A 60 degree angle of the arms of the Z is preferred, but the angle can be as acute as 20 degrees. The angles must be equal. When the incisions are made, two broad-based triangular flaps are formed whose bases are opposite each other. They are transposed and sutured without tension, forming another Z, turned approximately 90 degrees. The amount of the extension of the tissues will be the difference between the lengths of

the long and short diagonals of the parallelogram made by projecting lines across the bases of the triangles marked out by the Z, the short diagonal being the central line of the Z and the long diagonal being the distance between the distal ends of the arm lines.

Davis recommends the procedure for relaxation of scar tissue and prefers it for this to skin grafting or transplanting flaps from a distant part. It is simpler than most methods and utilizes tissue that otherwise would be discarded.

L. P. GUY.

### Orbit, Eyeball and Accessory Sinuses

EFFECT OF ELECTRIC STIMULATION ON OCULAR TENSION. P. B. ZARETSKAYA, *Am. J. Ophth.* **30**:589 (May) 1947.

Zaretskaya found that positive galvanism reduced ocular tension but that there was no such constancy from negative galvanism.

W. S. REESE.

PROGRESSIVE EXOPHTHALMOS. T. BARDRAM, *Acta ophth.* **22**:1, 1944.

The literature dealing with advanced progressive exophthalmos is surveyed. Three cases are reported, in all of which an increased output of gonadotropic hormone occurred in the urine. In 1 case the basal metabolism was increased, although there were no other signs of thyrotoxicosis. The pathogenesis of this condition is discussed and is believed by the author to lie in a disturbance of hormone correlation arising from removal of the thyroid gland.

O. P. PERKINS.

ORBITAL COMPLICATIONS FOLLOWING OPERATIONS ON PARANASAL SINUSES. E. GOLDTFREDSSEN, *Acta ophth.* **22**:401, 1944.

From a survey of case reports since 1902 and from a study of 8 cases of his own, the author concludes that orbital complications after operations on the frontal and maxillary sinuses are rare. They usually take the form of transitory orbital edema or paralysis of a solitary extraocular muscle. The complications following operations on ethmoid cells are severer and more frequent, taking the form of lesions of the optic nerve or orbital hematoma.

O. P. PERKINS.

### Retina and Optic Nerve

MODIFICATIONS OF THE FORMULA OF BLOOD IN THROMBOSIS OF THE CENTRAL RETINAL VEIN. THOMAS, CORDIER, PIERQUIN and HENRY, *Bull. Soc. d'opht. de Paris*, (Nov.-Dec.) 1946, p. 72.

The authors divide cases of thrombosis of the central vein into three types: those occurring in youth, in which an inflammatory origin is usual; those in which syphilis or tuberculosis is the etiologic factor, and those due to foci of infection. Basically, in the majority of cases in all three types there is angiosclerosis and often hypertension. Increase in

platelet count and also increase of red blood cell count are frequent findings. Treatment by roentgen therapy to reduce platelets and number of red blood cells may prevent further accidents. The use of dicumarol is not without danger.

L. MAYER.

MINIMAL RETINAL ARTERIAL HYPOTENSION IN FATAL BARBITURATE INTOXICATIONS. C. HENRY, Bull. Soc. d'opht. de Paris, (Nov.-Dec.) 1946, p. 76.

Henry reports on 3 patients who died from an overdose of barbiturates in which it was possible to measure the retinal arterial tension. Diagnostically, a low arterial tension may be an earlier sign in these cases than loss of the swallowing reflex. In all patients with coma such a measurement is indicated, and if found to be very low is strongly suggestive of barbiturate poisoning.

L. MAYER.

PATHOGENESIS AND TREATMENT OF RETINAL DETACHMENT OF TUBERCULOUS ORIGIN. A. POKROWSKY, Vestnik oftal. 25:17, 1946.

A review of the literature indicates that retinal detachment in tuberculosis of the eye is caused by changes in the retinal vessels: perivascularitis, hemorrhages and retinitis proliferans. Some authors believe that the changes in the vessel wall are caused (Lotin) not only by toxins but also by the tubercle bacilli.

Pokrowsky believes that prolonged tuberculosis of the choroid disturbs the nutrition of the retina and produces its degeneration in a broad sense, including degeneration of the vitreous. Although tuberculous detachment is of the exudative type and does not present a tear, slight trauma may lead to tear in the diseased retina. A history of such a case is given in detail.

The conclusions are as follows: 1. Retinal detachment with a tear may form in tuberculous chorioretinitis due to a slight, indirect trauma, and appear as a primary idiopathic detachment. A careful history, ophthalmoscopic and general examination will reveal the tuberculous origin of the detachment.

2. The presence of the tear in the detachment is an indication for a diathermy operation.

3. The positive results of the operation should not divert the attention of the ophthalmologist, and the specific tuberculous treatment should be continued.

4. In each detachment of the retina, the tuberculous causation should be kept in mind.

OLGA SITCHEVSKA.

ON THE DEPTH OF CAUTERIZATION IN SURFACE DIATHERMY, WITH SPECIAL REFERENCE TO DETACHMENT OPERATIONS. B. ROSENGREN, Acta ophth. 24:389, 1946.

The following excerpt is from the author's summary: A correctly balanced surface action is of importance in detachment operations done by

means of surface diathermy on the sclera. On the basis of his own observations, which indicated that effects of excessive strength could be obtained with electrodes of the size commonly employed, the author has made an experimental study of the depth of cauterization under different conditions. Cattle livers were used as test material. The results show that the depth of the effect is conditioned by these factors:

1. The depth of the effect is increased when the water content of the surface is high.

2. The depth of the effect is greater when diathermic cauterization is performed with a weak current for a relatively long period than when a strong current is allowed to act for a short time.

3. The larger the electrode, the deeper is the effect. If the degree of moisture on the surface and the time of coagulation are standardized, it is possible to regulate the depth of the effect quite accurately by using different electrodes. Visual judgment of the coagulation process appear to permit a relatively high degree of accuracy.

O. P. PERKINS.

### Tumors

LYMPHANGIOENDOTHELIOMA OF THE ORBIT SIMULATING A LACRIMAL GLAND. M. VERZELLA, *Riv. di oftal.* 1:343, 1946.

The author describes a case of lymphangioendothelioma of the orbit. The clinical picture, that of a neoplasm developing in the region of the lacrimal gland, led one to suspect at first a tumor of the gland itself. Histologic examination pointed to the exact diagnosis of the origin and nature of the neoplasm. Excision of the tumor was followed by rapid healing, without recurrence in more than two years.

G. B. BIETTI—J. J. LO-PRESTI.

ANGIOMA OF THE CHOROID. G. CRISTINI, *Riv. di oftal.* 1:374, 1946.

The author emphasizes the rarity of choroidal angioma and reports a case under his observation. He refers to clinical features which, within certain limits, can serve as diagnostic signs. He states that these are of congenital origin and that, according to the concept of di Marzio with regard to orbital angiomas, there is operative an initiative stimulus brought on by the changes in the circulation in the affected part.

The author discusses some features of the histogenesis of the choroid on the basis of his own observations on the histopathologic features of his case.

G. B. BIETTI—J. J. LO-PRESTI.

TYPES AND VARIANTS OF EPIBULBAR EPITHELIOMAS: A TYPICAL INVADING AND CACHEXIA-PRODUCING EPITHELIOMA AND A BARELY MALIGNANT EPITHELIOMA ARISING FROM THE KERATOCONJUNCTIVA (TYLOMA). M. VERZELLA, *Riv. di oftal.* 1:909, 1946.

The author describes 2 cases of epibulbar epithelioma, interesting because of the anatomicoclinical characteristics which distinguish them from the cases reported in the literature to date.



The first case was characterized by the extreme malignancy of the neoplasm. Three months after its excision, it recurred so rapidly that within a month it invaded almost the entire surface of the globe, the periorbital tissue, the ciliary body and the suprachoroidal space, perforated the globe in two places (at the limbus and the ora serrata) and metastasized to the regional lymph nodes and the internal organs, producing rapid cachexia and, finally, the death of the patient. The second case was one of an intermediate or a typical epithelioma with a benign clinical course, corresponding to that of a conjunctival tyloma.

The author presents the possibility that epitheliomas may arise from a preexisting tylomatous change, which, while not always innocuous because of the degenerative changes in the cornea it may cause, has a certain predisposition to develop into cancer.

The great shrinkage of the lesion with roentgen rays, diathermy or high frequency waves is the therapeutic test.

G. B. BIETTI—J. J. LO-PRESTI.

RETINOBLASTOMA IN A MAN AGED 48 YEARS. K. RASMUSSEN, *Acta ophth.* **21**:210, 1944.

A blind, irritable eye was removed from a man aged 48. Histologic examination revealed the presence of a retinoblastoma.

O. P. PERKINS.

A CASE OF RETICULUM CELL SARCOMA OF THE PLICA SEMILUNARIS. K. VAN WALBEEK, *Acta ophth.* **24**:183, 1946.

A man aged 58 had a reticulum cell sarcoma of the plica semilunaris. He died two years later of metastases of the skull. A summary of the literature on this condition is given.

O. P. PERKINS.

## Uvea

ANGIOID STREAKS. B. A. KLIEN, *Am. J. Ophth.* **30**:995 (Aug.) 1947.

Klien reports 6 cases of angioid streaks, including the histologic changes in two eyes. She concludes that the condition is based on abnormal fragility and opacification of the lamina basalis of the choroid. Previous studies have revealed that degeneration of the elastic portion of this membrane is the initiating factor, this corresponding to a general inferiority of the elastic tissue of the body as indicated by the frequent association with pseudoxanthoma elasticum and with severe degenerative vascular disease.

W. S. REESE.

## Vision

TWILIGHT VISION AND VITAMIN A. T. ANGIOS, *Rassegna ital. d'ottal.* **13**:11, 1946.

Angios has sought to improve twilight vision beyond the limits usually obtained after adaptation by administering vitamin A to normal per-

sons without vitamin deficiency. Previous experiments by other writers have yielded results which disagree with those of the author. Examinations were conducted on 51 persons of the same age without general or ocular defects and leading the same type of life. They were divided into three groups: The first worked strenuously for forty minutes on the telemeter daily; the second also worked daily for thirty minutes at a forced pace; the third carried on normal activities without special exertion. To avoid errors due to undeterminable factors, each group was subdivided into three subgroups, of which the first served as a control and the second and third as subjects for the experiment. The determinations were made in a room illuminated by reduced daylight admitted through the crack of a closed window. The constancy of the light was checked by a Leica light meter, observations being made only when the intensity was constant. Visual acuity was measured by Landolt rings after a forty minute adaptation. After a series of determinations showing constant results, 50,000 international units of vitamin A was administered to the second subgroup, and 100,000 vitamin A units to the third subgroup. Observations were repeated as before. The author shows by a series of tables and graphs that an improvement of twilight vision was obtained after administration of vitamin A, more evident when a dose of 10,000 international units was used, and specially in persons working at a forced pace. He ends by advising administration of vitamin A to all who must exhaust their threshold capacity, especially if it tends to lessen from fatigue or from long exposure to intense light.

G. B. BIETTI—J. J. LO-PRESTI.

### Vitreous

THE SUBSTITUTION OF CEREBROSPINAL FLUID FOR VITREOUS CLOUDED WITH OPACITIES. M. H. FRITZ, *Am. J. Ophth.* **30**:979 (Aug.) 1947.

Fritz reports 4 patients in whom cerebrospinal fluid was substituted for cloudy vitreous. The vision of the youngest was improved from light projection to 20/20-1. He had had a vitreous hemorrhage a year previously from an ocular contusion.

W. S. REESE.

### Sympathetic Ophthalmia

ON MENINGEAL REACTIONS IN SYMPATHETIC OPHTHALMITIS. L. CORCELLE, *Brit. J. Ophth.* **31**:366 (June) 1947.

Three cases of sympathetic ophthalmia are reported in which meningeal reactions were noted. In 2 of the cases the microscopic examination of the enucleated eye is stated to have shown the "inoculation chancre" described by Redslob. No histologic report is given in the third case.

The time of onset of lymphocytic meningitis is indicated by lumbar puncture, which may perhaps be regarded as contemporaneous with the appearance of clinical signs in the sympathizing eye.

W. ZENTMAYER.

A NEW SYMPTOM IN SYMPATHETIC OPHTHALMIA. L. GUGLIANETTI, *Ras-segna ital. d'ottal.* **13**:5, 1946.

Anatomic and pathologic studies of sympathetic ophthalmia have shown that in the initial stages of the disease the inflammatory process of the uvea is particularly pronounced in the posterior part, gradually diminishing in intensity anteriorly toward the ciliary body and posteriorly toward the macula.

The author has sought to demonstrate a diminution in the sensitivity of the retina in the zone under discussion (between the macula and the periphery) by means of campimetry.

In 3 cases of sympathetic ophthalmia he has demonstrated a ring scotoma, which was present only when the surrounding illumination was dim. The Maggiore perimeter, with targets of low intensity, served the purpose best.

The diminution in the light sense in the form of a ring scotoma is a new sign of early sympathetic ophthalmia.

G. B. BIETTI—J. J. LO-PRESTI.

SYMPATHETIC OPHTHALMIA FOLLOWING SUBCONJUCTIVAL RUPTURE OF THE SCLERA. C. E. LUGUE, *Arch. chileno de oftal.*, **2**:26 (Nov.-Dec.) 1946

A man aged 33 was examined three days after a blow was received on the right eye. A subconjunctival rupture of the sclera in the supero-external region was present. There was no hernia of the uvea or any superficial symptom which might suggest subconjunctival dislocation of the globe. A total hyphema prevented examination of the fundus. Vision was reduced to light perception. The ocular tension was low. Nine days later the patient was discharged. Two months later the right eye was blind, and the vision in the left eye was reduced to perception of hand movements. A diagnosis of sympathetic ophthalmia was made. The author points out that this complication is rare in cases of scleral rupture. Enucleation was not deemed advisable, and the usual treatment was given. The patient died of acute hepatic insufficiency, and it was impossible to obtain the eye for pathologic examination.

M. E. ALVARO.

### Therapeutics

SODIUM SULFACETIMIDE. W. L. BENEDICT and J. W. HENDERSON, *Am. J. Ophth.* **30**:984 (Aug.) 1947.

Benedict and Henderson found sodium sulfacetimide in a 30 per cent solution or a 10 per cent ointment safe for average clinical use. The solution gave better results, and the drug was more efficacious in acute varieties of catarrhal and purulent conjunctivitis.

W. S. REESE.

EXPERIMENTAL AND CLINICAL STUDY OF THE ANTISEPTIC ACTION OF MERBROMIN ["MERCUROCHROME"]. M. MAIONE, *Ann. di ottal. e clin. ocul.* **72**:114, 1946.

The author has begun a series of studies in vitro and in vivo to investigate the value of merbromin ("mercurochrome") in ophthalmic practice. The results obtained showed that the drug is active against the conjunctival flora and is effective in septic diseases of the globe and the adnexa.

G. B. BIETTI—J. J. LO-PRESTI.

PENICILLIN IN OPHTHALMOLOGY. S. BERRENCHEA and R. CONTARDO, *Arch. chilena de oftal.* **4**:12 (Jan.-Feb.) 1945.

After discussing the value of penicillin in treatment of various ocular diseases, the author summarizes the results in 32 cases, distributed as follows: chronic blepharitis, 8 cases; bacterial conjunctivitis, 16 cases; ser-piginous corneal ulcer, 3 cases; perforating wounds of the cornea, 2 cases; panophthalmitis, 2 cases, and iritis, 1 case. In every case the results were splendid. The local method of treatment is indicated with diseases of the lids, the lacrimal passages, the conjunctiva and the cornea. With diseases of the iris, systemic administration is preferred. For action on the aqueous humor, local treatment should be combined with sub-conjunctival injections or injections into the anterior chamber together with systemic treatment. With conditions of the vitreous, injections into this body should be added.

H. F. CARRASQUILLO.

VITAMIN P IN OPHTHALMOLOGY. P. MATA, *Arch. Soc. oftal. hispano-am.* **6**:1257 (Dec.) 1946.

Vitamin P is a complementary factor of vitamin C. In 1936 Szent-Györgyi and his associates proved that concentrated vitamin C obtained from lemons and oranges had some action on the pathologically increased permeability of the capillaries, whereas pure or synthetic ascorbic acid had no action whatever. They succeeded in isolating a crystalline substance, which they called citrin. This substance acted on the excessive permeability of the capillaries, and because of this action it was called vitamin P. In spite of its crystalline structure, it is not a simple substance, but an isomorphous mixture of its two component glucosides, hesperidin and eriodictyol.

Like vitamin K, its use is indicated in types of hemorrhages produced by hypothrombinemia. Scurvy, infections and anaphylactic vascular pur-puras were first treated with this vitamin. For its therapeutic use, the hemorrhage need not be due to a hypovitaminosis of any kind. Clinically, the beneficial effect of vitamin P has been proved in hemorrhages of uncertain origin. Thus, combined with treatment for the causative factor, its use is of value in focal iritis with hyphema, hemorrhages occurring in certain forms of severe iridocyclitis and diabetic iritis with rubeosis iridans.

The value of vitamin P also has been proved in the treatment of eczematous conditions of the lids accompanied with conjunctivitis and of

keratitis of scrofulous origin. Through its action on the permeability of capillaries, this vitamin has shown a beneficial effect on hemorrhagic retinopathies of nephritic origin. In cases of extensive retinal hemorrhages, subchoroidal extravasations and thrombosis of the central vein, it may be advantageously used. It may also be used in cases of juvenile recurrent hemorrhages of the vitreous.

The author has been in the habit of giving vitamin P combined with ascorbic acid as a prophylactic measure before surgical operations.

H. F. CARRASQUILLO.

USE OF VITAMIN K IN TREATMENT OF INTRAOCULAR HEMORRHAGES. N. AZAROVA, *Vestnik oftal.* 25:2, 1946.

Azarova observed 32 patients with intraocular hemorrhages of various cases. Fifteen patients had tuberculous choroiditis; of these, 4 patients had juvenile recurrent hemorrhages into the vitreous. Seven patients were elderly persons with hypertension and fragility of the vascular walls, and 10 patients received a preparation of vitamin K as a prophylactic measure before operative procedures.

The best results were obtained in the cases in which vitamin K was used before operations or in elderly patients with hypertension and fragility of the vascular walls. The patients with juvenile recurrent hemorrhages into the vitreous were not benefited by the vitamin K treatment; nor were the patients with tuberculous choroiditis. It is best to give vitamin K for only three days, as there was noted an increase of bleeding in some cases when the vitamin was given for ten days.

OLGA SITCHEVSKA.

### Toxic Amblyopia

ALTERATIONS OF THE VISUAL FIELDS IN TOBACCO AMBLYOPIA. L. HANBRESIN and C. SCHEPENS, *Bull. Soc. d'opht. de Paris*, Nov.-Dec. 1946, p. 79.

The authors found that 0.4 per cent of the patients brought into their clinic in occupied Germany had tobacco amblyopia. The central field as registered on the Bjerrum screen covered 30 degrees from fixation. The scotoma was for most cases central but often a cecocentral scotoma was noted. In severe cases a depression of the entire visual field with greatest encroachment in the superior temporal field was noted. The scotoma usually may be shown to follow the anatomic distribution of the papulomacular nerve fiber bundle.

L. MAYER.

## Book Reviews

**La neuro-angiomatose encephalo-faciale.** By A. M. Larmande. Price, 400 francs. Pp. 150. Paris: Masson & Cie, 1948.

This is a monograph on the condition commonly known in this country as the Sturge-Weber syndrome. A historical review of the subject is followed by the author's own observations on the syndrome as it is met with clinically. This is followed by a section on the theory of the physiopathology of the disease and its treatment. The volume is probably the most important monograph on the Sturge-Weber syndrome that has appeared.

FRANCIS HEED ADLER.

**Management of Binocular Imbalance.** By Emanuel Krinsky, M.D. Pp. 464, with 200 illustrations. Philadelphia: Lea & Febiger, 1948.

While the title suggests that this book deals with the heterophorias exclusively, it is concerned equally with the manifest, as well as the latent, deviations. For many years, the author has advocated a unique approach to the study of oculomotor disturbances. He believes that since the corneal light reflex is the most important objective landmark, the deviations of this reflex should be noted rather than the movements of the eye. All the observable phenomena are therefore presented from this point of view. While this thesis is supported by many good arguments, it is apt to be confusing at first to one accustomed to observe movements of the eye rather than movements of the light reflex, which obviously are in the opposite direction. This is a minor point, however, and not a justifiable criticism in view of the excellent illustrations. These are diagrammatic and for the most part have been drawn by the author. They are superb and do what an illustration is intended to do, i.e., make the text clear at a glance.

The first chapter is taken up with a consideration of the corneal light reflex. The next five chapters consider the anatomy and physiology of the ocular muscles. Chapter 6, dealing with the heterophorias, is especially commendable, since the author approaches this subject from the physiologic aspect. Chapter 7 deals with prisms, particularly the aspect of the effect of prisms on the corneal reflex. Chapter 9 is concerned with normal and abnormal binocular vision. The phenomena of normal and anomalous correspondence have been confused by so many writers, because of a wide variety of meanings in the use of certain terms, that most readers, like the reviewer, look hopefully into each new book on ocular muscles with the expectation of being enlightened. Unfortunately, the section on the corneal light reflex in retinal correspondence leads only to further confusion. Chapters 10, 11 and 12 are concerned with the examination of patients with binocular imbalance. Chapter 13, entitled "Neurological Considerations," deals with supernuclear and infranuclear ocular muscle palsies. Chapter 14 discusses the problem of squint in children. This chapter does not add anything to what is already known. In chapter 15 a number of miscellaneous topics are considered, such as occlusion, face

rotation and head rotation, visual skill in aviation and in industry, and ptosis. The last three chapters deal with the use of prisms, the stereoscope and surgical measures in treatment.

Taken as a whole, the book is useful in collecting this author's many contributions to the literature of squint, since nearly all of these are original in their point of view and many of them extremely valuable. While the reviewer would not advocate this book as a text for the student beginning his training, the experienced worker would find it worth while to review the whole subject of squint, using this book to obtain an entirely different point of view.

FRANCIS HEED ADLER.

**Psychodynamics and the Allergic Patient.** By Harold A. Abramson, M.D. Price not stated. Pp. 81, with 2 illustrations. Minneapolis: The Bruce Publishing Company, 1948.

The object of this book is to focus the attention of clinicians on the importance of emotional factors in the routine therapy of allergic conditions. The book is the outcome of a symposium, bringing together authorities in the field of psychiatry and allergy. It will be of particular interest to the ophthalmologist who has to treat allergic conditions.

FRANCIS HEED ADLER.

## News and Notes

EDITED BY DR. W. L. BENEDICT

### SOCIETY NEWS

**Annual Meeting of Oregon Academy of Ophthalmology and Otolaryngology.**—The tenth annual spring postgraduate convention of the Oregon Academy of Ophthalmology and Otolaryngology will be held in Portland, June 19 to 24, 1949. Another fine program has been arranged by the Oregon Academy and the University of Oregon Medical School. There will be four guest speakers—men outstanding in their respective fields: Dr. Lawrence R. Boies, professor of otolaryngology at the University of Minnesota Medical School, Minneapolis; Dr. Leland Hunnicutt, associate clinical professor of otolaryngology at the University of Southern California School of Medicine, Los Angeles; Dr. James H. Allen, professor of ophthalmology at the State University of Iowa School of Medicine, Iowa City, and Dr. Edmund B. Spaeth, professor of ophthalmology at the University of Pennsylvania Graduate School of Medicine, Philadelphia.

There will be lectures, clinical demonstrations and ward rounds.

Preliminary programs will be out about May 1. They may be secured, with further information, from Dr. David D. DeWeese, secretary, 1216 S.W. Yamhill Street, Portland 5.

In order that the course may be made more personal and practical, registrations will be limited to 125.

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## THE BLINDSPOT SYNDROME

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IN 1947 a squint syndrome was described in which the physiologic blindspot, created by the optic papilla, seems to play an especial role.<sup>1</sup> Recognition of this syndrome resulted from a study of the field of binocular vision in 296 cases of concomitant esotropia in older children and adults. For distant fixation the physiologic blindspot of the deviating eye was found to overlies the point of fixation in 80 cases; i. e., the deviation was 12 to 18 degrees. In most of these cases the physiologic blindspot was only part of a suppression scotoma and its position was inconstant; however, there were 7 cases in which it seemed probable that the physiologic scotoma provided the essential mechanism for the alleviation of diplopia and played an important role in maintaining the esotropic state. These 7 cases had in common certain symptoms and signs, and the responses to treatment and clinical courses were similar. This group of cases seemed to represent a clinical entity, which was designated as the "blindspot syndrome" (fig. 1). Since the initial report of 7 cases was submitted for publication, an additional 95 cases have been observed in which the physiologic blindspot of the squinting eye seemed to play the major role in alleviation of diplopia, i. e., acted as a central scotoma in the field of binocular vision. It is the purpose of the present report to review this larger series of cases in order to establish more definitely the circumstances in which this mechanism develops and to determine how it influences the clinical features, course and treatment of concomitant esotropia.

To appreciate the possible role of the blindspot in concomitant esotropia, it is necessary to understand the mechanism of diplopia. In the presence of normal retinal correspondence and in the absence of suppression, diplopia theoretically results whenever grossly dis-

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1. Swan, K. C.: A Squint Syndrome, *Arch. Ophth.* **37**:149-154 (Feb.) 1947.



parate retinal areas receive a similar stimulus. In reality, most persons are aware of seeing double only the object of conscious regard, i. e., the point of fixation and the immediately surrounding area. Diplopia in the peripheral fields may play an important role in the mechanism of binocular vision, but the normal person is little aware of peripheral double images when the eye is mechanically displaced. He may alternately fix with either eye, but his attention is on diplopia of the "object or area of regard."

Most patients with long-standing, untreated concomitant esotropia are not aware of diplopia because the object or area of regard is perceived monocularly. Travers<sup>2</sup> expressed the belief that this monocular perception of the object of regard was due to suppression of the image

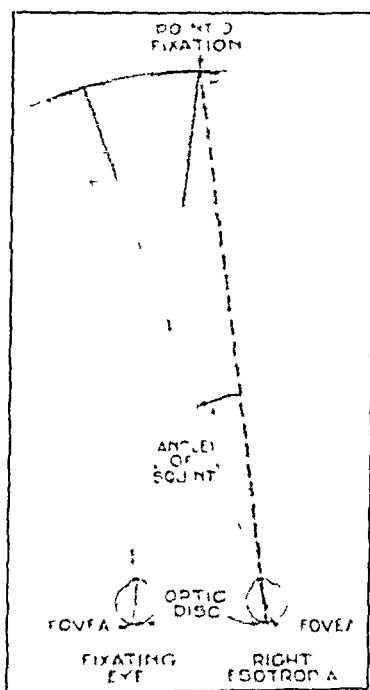


Fig. 1.—Mechanism of the blindspot syndrome, characterized by periodic diplopia, concomitant esotropia, physiologic blindspot of the squinting eye overlying the point of fixation, hypermetropia or anisometropia, normal retinal correspondence and usually some amplitude of fusional movements.

of the peripheral retina of the squinting eye; however, in cases of the blindspot syndrome rays of light from objects fixated by the fovea of the fixating eye largely fall on the optic papilla of the squinting eye. In such instances an absolute scotoma, the physiologic blindspot, is provided by nature to cover, at least partially, this area of regard.

#### LOCALIZATION OF BLINDSPOT OF DEVIATING EYE

There are several methods of localizing the physiologic blindspot of the deviating eye in the field of binocular vision. It is obvious that

2. Travers, T. a'B.: The Origin of Abnormal Retinal Correspondence, *Brit. J. Ophth.* 24:58-64 (Feb.) 1940.

in most cases an esotropia of 12 to 18 degrees results in the areas of the field of binocular vision corresponding to the fovea of each eye being overlapped by the physiologic blindspot of the opposite eye. In cases of the blindspot syndrome, this deviation may be a degree or two greater or less, apparently in accordance with whether or not there is a peripapillary area of retinal suppression to enlarge the scotoma in the field of binocular vision. A considerable degree of hypertropia may also occur. For near fixation, the deviation of the eyes from parallelism would have to be correspondingly greater if the blindspot were to be utilized for the alleviation of diplopia but the deviation as measured by the cover test would remain unchanged. Stated otherwise, if a patient has concomitant esotropia of 10 to 20 degrees, rays of light from the area of regard are largely falling on the blindspot of the

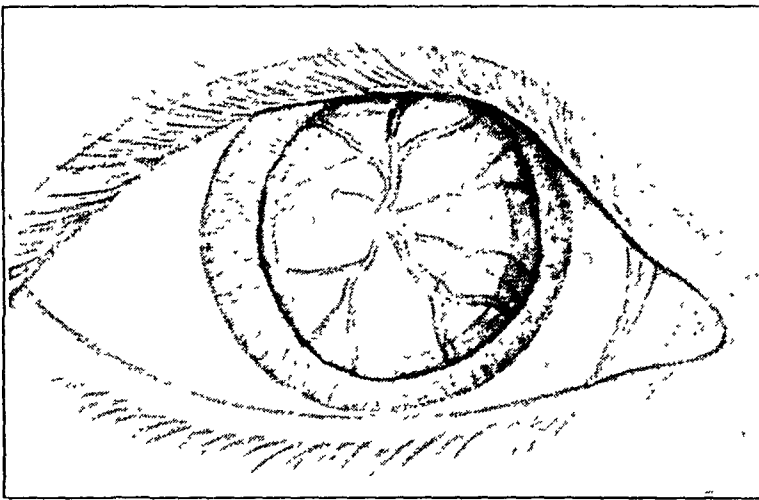


Fig. 2.—Viewed with the ophthalmoscope at a distance of 6 to 10 inches (15 to 25 cm.), the optic papilla of the deviating eye appears to fill the pupillary area in a case of the blindspot syndrome.

squinting eye and the object of regard, at least in part, is being viewed monocularly.

A second means of determining the position of the blindspot is ophthalmoscopy. While the patient fixates a distant point of light, the examiner places himself directly in front of the deviating eye and focuses on the fundus from a distance of 6 to 10 inches (15 to 25 cm.). In cases of the blindspot syndrome, an enlarged image of the nerve head will almost completely fill the pupillary area (fig. 2).

A third method of determining the usual position of the blindspot is to plot the field of vision of the deviating eye while the other eye is fixating. To do this, it is necessary to separate the images of the two eyes, either by a mirror and two screens or by filters and twin projectors. Either polaroid or red and green filters of the type described by Lancaster may be used with two projectors to separate the targets

presented to the two eyes.<sup>3</sup> The blindspot of the squinting eye is plotted on a large screen in an illuminated room to simulate as nearly as possible the usual visual conditions. With the Lancaster red and green filter-twin projection system, it frequently has been possible to plot the central field of binocular vision in children of preschool age by the method to be described.

The degree of esotropia is measured in the usual manner and the patient is asked, while wearing the color filters, to adjust the direction of one of the projectors until the red and green images appear superimposed on the screen. In the presence of normal retinal correspondence the separation of the targets on the screen will be in accordance with the deviation of the patient's eyes. Then the blindspot is localized in the monocular field of vision with particular reference to the distance between the point of fixation and the center of the blindspot. If

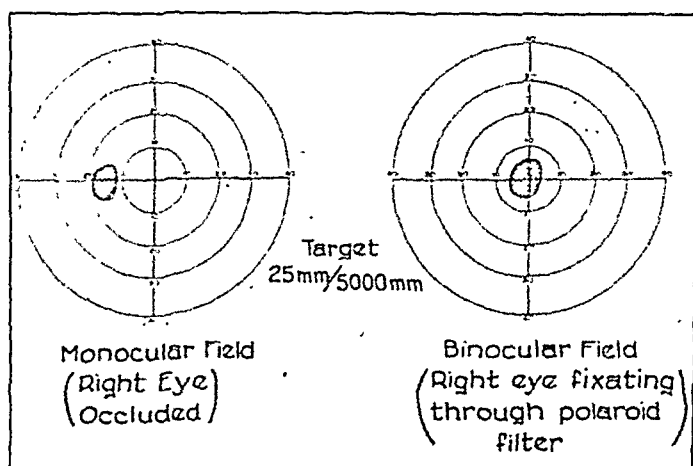


Fig. 3.—Position of the physiologic blindspot of the deviating eye in a case of concomitant left esotropia of 14 D.

this angle is equal to the previously determined deviation of the eyes, it is evident that the blindspot of the squinting eye overlies the point of fixation in binocular vision. Further confirmation can be obtained by actually localizing the blindspot in the field of binocular vision. In cases of the blindspot syndrome, an absolute scotoma the size and shape of the blindspot can usually be demonstrated to overlie the point of fixation (fig. 3). For this reason, only one target is visualized by the patient when the two targets are superimposed on the screen (fig. 4).

An adjustable haploscopic device, such as the major amblyoscope, provides still another means of localizing the blindspot of the squinting eye. In most cases of the blindspot syndrome an area of monocular perception measuring 5 to 8 degrees in horizontal diameter will be

3. Lancaster, W. B.: Detecting, Measuring, Plotting and Interpreting Ocular Deviation, *Arch. Ophth.* 22:867-880 (Nov.) 1939.

found when the instrument is adjusted to the region of orthophoric position (fig. 5); however, this is not a constant finding because the instrument gives the patient a sensation of nearness and, therefore,

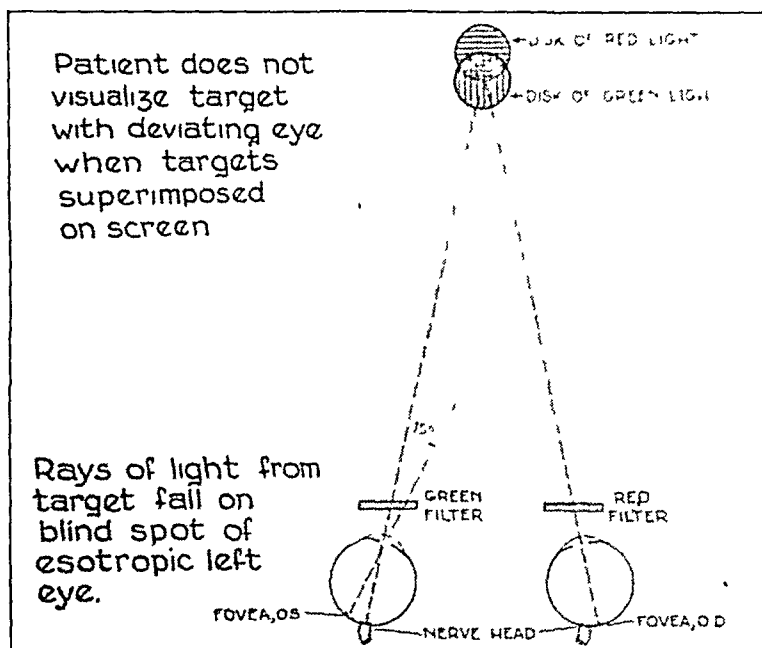


Fig. 4.—Use of red-green filter-projection system to localize scotoma of the deviating eye in a case of the blindspot syndrome.

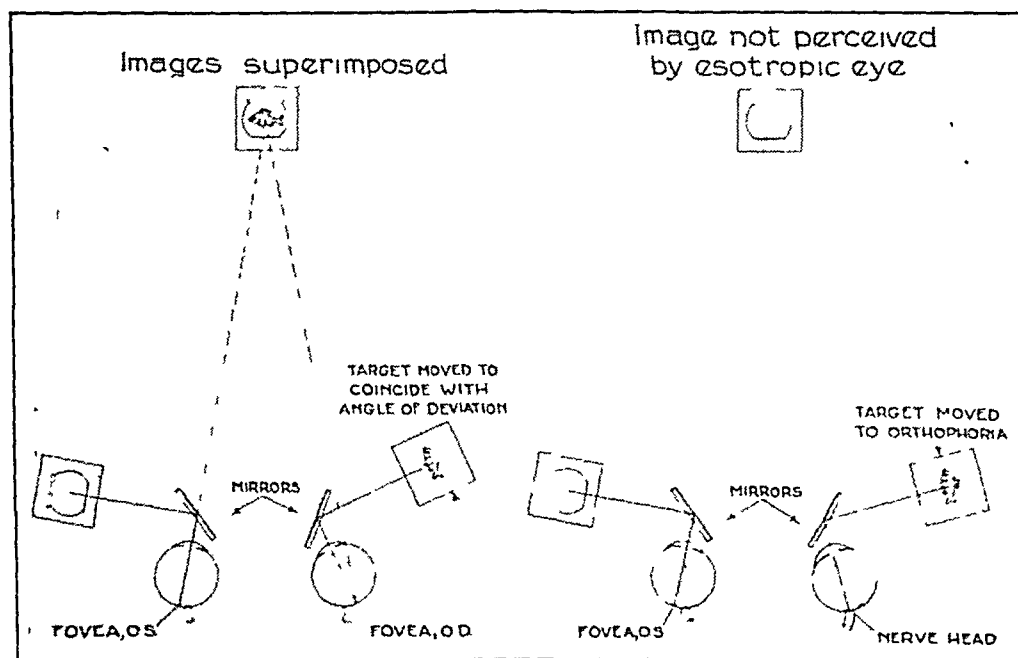


Fig. 5.—Examination with the major amblyoscope in a case of the blindspot syndrome, with esotropia of 15 degrees.

often stimulates a position of greater esotropia than is present under usual visual conditions. Moreover, accurate plotting of the vertical measurements of the blindspot is awkward with the major amblyoscope.

For these reasons, the major amblyoscope is less satisfactory than filter-twin projection systems for localization of the blindspot of the deviating eye.

In some patients it has been possible to measure the scotoma created by the blindspot by using prisms to create diplopia, i. e., by determining the size of prism necessary to shift rays of light from the point of fixation off the blindspot of the deviating eye. In many patients, however, prisms stimulate disjunctive movements, apparently to maintain the blindspot as a central scotoma. This occurs most commonly with prisms base out. These pseudofusional movements seem further evidence of the functional role played by the blindspot as a central scotoma.

It might be coincidental that, in a given case, the physiologic blindspot of the squinting eye overlies the object of regard in the field of binocular vision; therefore, it is essential to demonstrate that the blindspot actually is a factor in the alleviation of diplopia by the induction of double vision when the blindspot is deviated to another position. Stated otherwise, it could not be assumed that the blindspot of the squinting eye served a functional purpose as a central scotoma simply because the eye was so deviated that the blindspot would overlie the object of regard in the field of vision. It would be necessary to prove this supposition by using prisms or other devices to displace the blindspot of the squinting eye from the central area, and thereby creating double images of the object of regard in ordinary visual circumstances.

#### OBSERVATIONS

Using the aforementioned methods of examination, my associates and I observed in eight years 102 cases of esotropia in which a central position of the physiologic blindspot of the deviating eye seemed essential for the alleviation of diplopia. In general, these cases had in common the symptoms and signs which already have been designated as the blindspot syndrome.

The commonest complaint was that of a "slight cross-eye," but the most significant symptom was periodic diplopia. This history was seldom volunteered because in only a few cases was the diplopia annoying, but it could be elicited in 75 of the 102 cases. In every case homonymous diplopia could be created under ordinary visual conditions by the use of prisms just large enough to shift the rays of light off the blindspot of the squinting eye.

The most obvious sign was concomitant esotropia, of 10 to 20 degrees. The average deviation was 14 to 16 degrees for distant fixation. The deviation from parallelism was proportionately greater for near fixation, but greater variations were found.

In the first report of blindspot syndrome, it was observed that hypermetropia or anisometropia was present in all 7 cases. Analysis

of the refractive error in the additional series of cases seems to confirm the importance of this observation. Of the 102 cases, hypermetropia of more than 2 D. or anisometropia of more than 1 D. was present in 62, a higher degree and higher incidence of these refractive errors than is generally reported to occur with esotropia.<sup>4</sup> This suggests that the hypermetropia or anisometropia is a common part of the blindspot syndrome, but analysis of a larger series of cases, with a concurrent study of the refractive error in a control series, will be necessary definitely to establish this fact.

Normal retinal correspondence seems a consistent feature of the blindspot syndrome. It could be demonstrated by the usual methods of examination to be present in all cases.<sup>4</sup> In some of our cases of anomalous correspondence, rays of light from the point of fixation seemed to fall on the blindspot of the esotropic eye, but diplopia could not be elicited under ordinary visual conditions in a single case of this group when the blindspot of the deviating eye was displaced from the central area. Our studies of the role of the blindspot in anomalous correspondence are not yet conclusive; however, they indicate that, although the physiologic blindspot may function as a part of the suppression scotoma, it does not play as important a role in the alleviation of diplopia as in cases of normal retinal correspondence.

In the initial orthoptic examination, the images of the two eyes could be fused into a single mental impression in less than one-half the 102 cases of the blindspot syndrome, and only a few had fusional movements of appreciable degree when the targets were adjusted to their deviation on a haploscopic device, such as the major amblyoscope; however, this sensory and motor fusional ability could be established in all the remaining cases in which orthoptic training was feasible. Good fusional potentialities can, therefore, be considered a part of the blindspot syndrome.

The symptoms and signs of the blindspot syndrome in the larger series of cases seem the same as in the initial group of 7 cases. An analysis of the circumstances in which this syndrome develops is of significance in determination of the role of the physiologic blindspot in esotropia.

In 32 cases in which there was no previous treatment the blindspot syndrome was evident on admission. In 22 of these cases there was an average spherical refractive error which was slightly less than 3 D. of hypermetropia with an associated astigmatism of approximately 1 D. The consistent finding of an appreciable degree of hypermetropia would seem to indicate that this refractive error was an important factor in the development of esotropia in these cases. The onset of

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4. Swan, K. C.: Definition of Anomalous Retinal Correspondence, *Am. J. Ophth.* **28**:58-61 (Jan.) 1945.

esotropia in this group of cases was also of significance. In about one-half the cases the first manifestation of anomaly was a periodic esotropia, becoming manifest at  $2\frac{1}{2}$  or 3 years of age in association with fatigue or illness. In the other one-half the onset of esotropia was early in infancy. In several of the latter group no treatment was given because during the first few years of life the esotropia seemed to be improving spontaneously. In these cases it is likely that the patients initially had a considerable amount of esotropia and then slipped into the "blindspot" syndrome when the deviation decreased.

In a second group, of 18 cases, the "blindspot" syndrome was not evident on admission. All the patients were children, with an average age of  $7\frac{1}{2}$  years. In these children the blindspot syndrome was not definitely acquired until correcting lenses were prescribed in our clinic. On admission, the average deviation was from 25 to 27 degrees of esotropia for distant fixation, but the deviation for near fixation was considerably greater. The average amount of hypermetropia in these cases was larger than that found in the remaining 82 cases of the blindspot syndrome, averaging almost 3.5 D., with an average of 1.25 D. of astigmatism. A history of diplopia was elicited in one third of these cases during the first week after glasses were prescribed. It is apparent from this group of cases that an appreciable number of patients with so-called accommodational squint who have a relatively large degree of esotropia slip into the blindspot syndrome when the prescription of correcting lenses effects only a partial reduction of the deviation.

In 17 cases of esotropia the blindspot syndrome developed after an operation which did not fully correct a deviation of 25 degrees or more for distant fixation. In 16 of the 17 cases normal retinal correspondence was evident before operation, and in the remaining case correspondence became normal after surgical intervention. For comparative purposes 98 cases of esotropia with anomalous correspondence were studied in which operation had been performed for purely cosmetic purposes. With the exception of the 1 case in which correspondence became normal after operation, in none of this group could it be demonstrated that the patient was utilizing the blindspot after operation for the alleviation of diplopia.

In a fourth group, of 8 cases, the blindspot syndrome seemed to develop in association with the establishment of normal retinal correspondence. In 2 of these 8 cases normal retinal correspondence developed during periods of alternate monocular occlusion. In the other cases occlusion and "macular massage" were required. With the development of normal retinal correspondence and the discontinuance of occlusion, the eyes acquired the typical deviation of the blindspot syndrome, and diplopia could be created with prisms displacing the blindspot of the squinting eye from the central area.

In another group, of 4 cases, the blindspot syndrome developed after the correction of amblyopia in the esotropic eye. In 1 of these cases esotropia had not been noticeable prior to the prescription of an occluder by another physician, who sought to improve visual acuity in the amblyopic eye. After six months of total occlusion, the ophthalmologist observed that visual acuity had improved from 20/200 to 20/30 in the affected eye, but that esotropia had developed and the child had periodic diplopia. On admission the child had all the aforementioned signs and symptoms of the blindspot syndrome. In the other 3 cases a gross esotropia associated with visual acuity varying from 20/70 to 20/300 in the deviating eye was present on admission. Prolonged occlusion in these cases markedly reduced the size of the suppression scotoma in the field of binocular vision and improved visual acuity to 20/25 in 2 cases and to 20/50 in the third case. In none of these cases

*Circumstances of Development of the Blindspot Syndrome*

	No. of Cases
Associated with uncorrected refractive error.....	22
Following prescription of glasses for accommodative esotropia.....	18
Following partially effective operation for esotropia.....	17
Associated with establishment of normal retinal correspondence.....	8
Associated with correction of amblyopia.....	4
Undetermined.....	33
Total.....	102

was the blindspot syndrome evident until weeks after occlusion was discontinued.

In 30 cases it was not possible to determine the circumstances in which the blindspot syndrome developed, because in most of them some type of treatment had been received prior to admission. These observations, summarized in the accompanying table, indicate that the blindspot may develop as an initial process in association with an uncorrected hypermetropic or refractive error, but that, in the presence of normal retinal correspondence and with an appreciable degree of simultaneous binocular perception, patients with large degrees of esotropia frequently begin to use the physiologic blindspot of the squinting eye as a central scotoma when the deviation is reduced either by surgical intervention or by glasses. Moreover, it seems that a blindspot syndrome may develop in esotropic patients when normal retinal correspondence is first established or when amblyopia and suppression are disrupted by occlusion.

The period of observation is too short for one to determine with certainty the course of the blindspot syndrome, but it seems that once this mechanism for the alleviation of diplopia is established,



unless modified by treatment, it remains unchanged for relatively prolonged periods. Twelve of the 102 patients were adults, and, of this group, 4 had become so well accustomed to their condition that they did not seek correction of the esotropia. One man, aged 44, could remember having had periodic diplopia since childhood. Another adult, with a similar history, is a physician who has been under observation for nearly four years. During this period, the signs and symptoms have remained unchanged. In addition to this group of adults, 11 children have been observed over a period of one and one-half to three years for whom, for various reasons, no treatment other than correction of refractive errors has been prescribed. In these patients the condition has remained unaltered despite the fact that these patients are all rapidly growing, with decreasing refractive errors and changing orbital structure.

That the mechanism of the blindspot tends to remain constant is also evident in analysis of the results of attempted cosmetic surgery in well established cases of the blindspot syndrome. In 24 cases surgical correction was attempted without orthoptic training or measures other than correcting lenses. In only 7 of these cases were there spontaneous development and maintenance of single binocular vision over a period longer than six months. In most of the remaining 17 cases postoperative diplopia was immediately evident, and in all but 5 cases the blindspot syndrome redeveloped within a period of nine months. The significance of this observation will be discussed further in relation to treatment.

The prognosis for the blindspot syndrome is excellent when the condition is recognized and properly treated. Of the 102 cases, therapy was carried to completion in only 38; that is, single binocular vision with bifoveal fixation, stereopsis, a comfortable reserve of fusional movements and establishment of a satisfactory accommodation-convergence relationship under the usual visual conditions was effected. The average period of treatment was seventeen months. In 25 cases treatment is now going on and progress is satisfactory. In a number of cases orthoptic training is being deferred until the child is old enough to cooperate fully with orthoptic measures. Finally, in 10 cases, including 4 of adults, an attempt to restore single binocular vision did not seem justified. In most of these cases the deviation of the eyes was not conspicuous; the patients had adjusted themselves to the periodic diplopia and could perform their visual tasks comfortably. In several of these instances a wide angle kappa in each eye made an actual deviation of the lines of vision of about 15 degrees appear inconspicuous.

Of greater significance than the total number of cases in which single binocular vision has been restored is the fact that not a single

failure has resulted in any case in which the patient was of average intelligence and cooperated in treatment, and in which there was opportunity to carry the treatment to completion.

The number of patients treated is large enough and the period of observation following restoration of single binocular vision sufficiently prolonged to indicate clearly that a combination of corrective measures is essential for the effective treatment of the blindspot syndrome. Exceptions are made to fit the circumstances in the individual cases, but the routine which seems most successful is as follows: As the first step in treatment, the refractive error is fully corrected, and the results are observed for a few days or several weeks. A longer period does not seem justified, for in only 1 of 27 cases in which no previous treatment had been given did the prescription of glasses alone result in the establishment of single binocular vision.<sup>5</sup> This favorable effect became evident within a few days. If correcting lenses create diplopia which cannot be overcome by the fusion mechanism, it is our custom to prescribe a monocular occluder to prevent the patient from slipping back into the blindspot syndrome or acquiring a suppression scotoma before further corrective, e. g., surgical measures can be undertaken.

Muscle surgery seldom seems fully effective unless the patient has an adequate reserve of fusional movements to maintain single binocular vision when the deviation is corrected. The best results have been obtained when operation has been deferred until an appreciable amplitude of fusional movements has been established by orthoptic training. This is administered in the clinic with the major amblyoscope, because the deviation is usually too great to permit the use of simple home training devices, such as the Brewster-Holmes stereoscope or prisms. In a few instances, as little as five or six hours of training, divided into short periods, has been required to establish a wide range of convergence and divergence, with control of accommodation. In a few extreme cases, five or six months of training, with sessions two or three times a week, have been required.

When ample fusional movements have been established, surgical correction of the deviation is conducted in accordance with established principles. It has been our custom to proceed cautiously and to err on the side of undercorrection, but in those few cases in which a slight overcorrection was done the patients have seemed to progress most favorably in their postoperative course. This was to be expected, because it is generally easier to build up the convergence to overcome an exophoria than it is to increase the amplitude of divergence to

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5. In this case a considerable esophoria has persisted during the few months that the patient, a 12 year old girl, has been observed. This patient is receiving intensive orthoptic training.

overcome an esophoria. On the other hand, a gross overcorrection is to be avoided. In 1 case the postoperative deviation was 10 D. of exophoria. The child was able to overcome this deviation only with considerable accommodative effort, and even after extensive training was still annoyed by spasms of accommodation after a relatively short period of reading. Orthoptic training may or may not be necessary after operation to establish an adequate reserve of fusional movements and a proper accommodation-convergence relationship. In summary, the optimal degree of surgical correction of the deviation in cases of the blindspot syndrome remains to be established by further experience, but it would seem that correction of the refractive error, establishment of ample fusional ability by orthoptic training and full or slight overcorrection of the esotropia by surgical measures produce most effective immediate results. Another decade will be required to determine the long range results.

#### COMMENT

It has been the purpose of this report to call attention of other ophthalmologists to the possible role played by the physiologic blindspot in cases of concomitant esotropia and to stimulate further investigation. The cases reported are inadequate in number and the period of observation is not sufficiently prolonged to permit one to speak of this role with finality. In a mechanism which is as complex as binocular vision, there are certain to be factors which have been overlooked. Nevertheless, the evidence that has been compiled in this study is indicative that the physiologic blindspot plays an important role in the alleviation of diplopia in certain cases of esotropia. The term blindspot syndrome has been employed as a means of distinguishing this group of cases for further study in varying circumstances and with different technics.

This study indicates that the blindspot syndrome is relatively common either as an initial condition or as a result of inadequate treatment of larger degrees of esotropia; but no conclusions as to the exact incidence of the syndrome can be drawn from this series of cases. Not only is our series of cases relatively small, but it includes an appreciable number of cases recognized by other ophthalmologists as belonging to the blindspot syndrome, and therefore referred to the University of Oregon for study.

A fact which has become evident in the study of a larger series of cases than were included in the initial report is that it is in distant fixation that the blindspot plays its greatest role in the alleviation of diplopia. In a patient with the blindspot syndrome the deviation for fixation at a distance of 5 meters or greater is surprisingly constant, and the position of the blindspot in the field of binocular vision can be demonstrated to lie constantly in the central field. On the other

hand, localization of the blindspot in the field of vision for near fixation usually is more variable. In some patients accommodative adduction fatigue seemed to play an important role in this variability; and, as a result, several reported an annoying diplopia after doing close work for short periods. In others it was evident that mechanisms other than the blindspot, such as excessive adduction of the nonfixating eye, would occasionally play a role in the alleviation of diplopia for near fixation.

In the blindspot syndrome, it is evident that the fovea of the squinting eye is covered by the physiologic blindspot of the fixating eye; consequently, there are two areas of monocular macular perception in the field of binocular vision in a case of the blindspot syndrome. A question which has frequently arisen in relation to this syndrome concerns what happens to the image perceived by the nonfixating fovea. In a number of more cooperative patients with the blindspot syndrome, it was possible to study this relation. When similar targets were presented to the foveal regions on an otherwise blank screen, they were fused; but when dissimilar, conflicting targets were presented, a rather pronounced dominance of one eye was frequently noted and retinal rivalry often could not be demonstrated. One patient occasionally noted a dim second image, different from the object of regard, superimposed on the point of fixation. On examination this proved to be the image perceived by the foveal area of the squinting eye. As yet these studies have been too few to be conclusive, but they indicate that a strong dominance of the fixating eye may be a common feature of the blindspot syndrome. Whether or not a true functional scotoma constantly occurs in the foveal region of the deviating eye, or whether the foveal region simply drops to the level of the surrounding peripheral retina with inattention, remains to be definitely established.

#### SUMMARY

In a large series of cases of esotropia observed in the clinics of two medical schools, 102 were found to have in common certain symptoms and signs which have been designated as the blindspot syndrome.

Periodic diplopia, a concomitant esotropia of 10 to 20 degrees, physiologic blindspot of the deviating eye overlying the area of regard, hypermetropia or anisometropia, normal retinal correspondence and potentialities for single binocular vision constitute the blindspot syndrome.

In this syndrome the eye is deviated into such a position that the physiologic blindspot of the esotropic eye overlies the point of fixation and the immediately surrounding area (area of regard) in the field of binocular vision. This seems to provide the essential mechanism for the alleviation of diplopia. Diplopia can be created in every instance

by shifting the blindspot off the central area with prisms or some haploscopic device.

The blindspot syndrome may develop spontaneously in association with an uncorrected refractive error. It may also be acquired after partial correction of a larger degree of esotropia, either by glasses or surgically. Occasionally it may develop after a period of occlusion of an amblyopic eye or in association with the establishment of normal retinal correspondence. The blindspot syndrome does not seem to develop in the presence of anomalous retinal correspondence; at least, it cannot be demonstrated to play a role in the alleviation of diplopia in such circumstances.

The prognosis for the restoration of single binocular vision in ordinary circumstances seems excellent in cases of the blindspot syndrome, provided that treatment is adequate. Glasses, surgical intervention or orthoptic training alone is seldom effective. It is necessary to correct the refractive error, to establish an ample range of fusional movements before operation, to correct fully the deviation by surgical means and then to follow operation with orthoptic training in order to establish a reserve of fusional movements adequate to overcome any residual deviation without undue stress on the accommodation-convergence mechanism. An attempt to restore normal binocular vision does not seem justified in an older patient who has visual comfort and in whom a large angle kappa makes the esotropia inconspicuous.

The blindspot syndrome has been described not as a fully established clinical entity but, rather, as a means of calling attention of other ophthalmologists to cases of concomitant esotropia in which the physiologic blindspot of the squinting eye seems to play an especial role in the alleviation of diplopia. It is hoped that study of patients with this disorder in varying circumstances, with different technics and by other ophthalmologists will determine more fully the clinical significance of this mechanism.

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#### ABSTRACT OF DISCUSSION

DR. FRANCIS HEED ADLER, Philadelphia: Dr. Swan has made a valuable contribution in pointing out that this syndrome can be cured in the majority of instances if the treatment is adequate. As a matter of fact, the syndrome may arise in some cases because of inadequate treatment. He has outlined the features which characterize the syndrome, the so-called accommodational squint; they are: an esotropia which is of a small angle, generally under 15 degrees, and concomitant hypermetropia; normal retinal correspondence, and potentialities of binocular single vision. In addition, the two characteristics Dr. Swan pointed out, which are necessarily present in order that the case may be placed in this subgroup of accommodational squint, are (1) that the

patient have periodic diplopia and (2) that diplopia can be elicited by displacement of the image from the blindspot in the squinting eye with prisms. This syndrome is not peculiar in its origin but can be explained by a relatively simple mechanism. A child with an esotropia of 12 to 17 degrees in the horizontal meridian has at all times a natural protection against diplopia because the image on the squinting eye falls on the blindspot of the optic nerve and corresponds with the fixation of the nonsquinting eye; therefore, he is continuously protected against diplopia. One of two things happens: As a result of his growing older, the angle of squint becomes less in some cases, presumably because his hypermetropia decreases. If, then, for natural causes, the angle of squint becomes less, the correspondence of the fovea in the fixing eye to the blindspot is no longer maintained. On the other hand, if the child is operated on later in life, after the age of 5 years, he is presented with a new situation; if the operation is not entirely complete and does not result in a fovea-to-fovea relation, the child is faced with the choice of having diplopia and accepting it, of learning suppression or of returning to his previous angle of squint.

In Dr. Swan's first series of cases, which he reported a few years ago, there was no patient under the age of 8 years. The diplopia came on at about school age, and it was obvious that the reason, in the cases in which it came on of itself, was that the angle of squint had diminished; the child was now presented with diplopia at a later age and had to learn suppression. Suppression is not easy to learn after the age of 5; so this syndrome appears after this age.

In those cases in which the condition followed operation, the surgical treatment was inadequate. In all cases which the author reported previously, the surgical measures were quite inadequate. He cured the patients by orthoptic therapy and (to me this is more important) by adequate surgical means. The point which I wish to bring out, however, is that one should recognize this condition and give adequate surgical treatment prior to the age of 5 years, and that if operation is not done prior to this age, and the patient given the chance to learn suppression, or at least to restore a fovea-to-fovea relation, one should recognize the condition when it arises, which it will at about the age of 7 or 8 years, with the complaint of diplopia. One then should carry out orthoptic treatment and adequate surgical measures. I should like to ask Dr. Swan the average age of the patients in the present series and the age of the youngest patient in the series.

DR. HERMANN N. BURIAN, Boston: The excellent paper which Dr. Swan has presented demonstrates again the fruitfulness of the physiologic approach to problems of ocular motility. The paper invites discussion from two points of view: (1) the facts and observations and (2) the interpretation of the facts. As a report of facts and observations it is outstanding for accuracy. This is in contrast to many papers on strabismus, in which the data leave much to be desired with respect to both accuracy and completeness. As an interpretation of the results, as to how the peculiar position of the blindspot influences the clinical features, course and treatment, there is room for discussion.

One may assume the case of a young child who is hypermetropic and who accommodates and overconverges in order to see clearly. If the child acquires strabismus, he will also experience diplopia. Heretofore, two ways have been known in which the child can rid himself of the diplopia: He may learn to suppress the unwanted image, or he may learn to localize the unwanted image in the more or less close vicinity of the fixated object; he may develop what is known as anomalous correspondence. Dr. Swan has shown us that there is a third way of alleviating diplopia. If the angle of squint, the hypermetropia and all other etiologic factors are such that the blindspot covers the object of regard, the visual problems of the child are solved; he does not have to look for further adjustments.

In cases in which this blindspot syndrome has existed since infancy or early childhood, the interpretation of the other clinical features offers no problem. These features are the absence of suppression scotomas in the binocular field of vision, normal retinal correspondence and a fair degree of binocular cooperation and an excellent functional result following properly conducted treatment.

One would not expect patients who have always had the blindspot syndrome to suppress or develop anomalous correspondence; there is no call for it. Also explained is the remarkable percentage of functional cures in cases of this syndrome. If therapeutic measures succeed in eliminating the deviation, all that is left is to start the patient on the road to normal binocular vision. Surely, cases of this type will be relatively rare, for special conditions are required, one of them being great stability of the angle of squint. According to Dr. Swan, there is a sizable number of patients who originally had a larger angle of squint and who acquired the blindspot syndrome when the angle decreased, either spontaneously or owing to therapeutic measures. In these patients, in whom the blindspot began to overlie the object of regard at a relatively late date, this course could not explain the prevalence of normal retinal correspondence and the absence of suppression scotomas. One must assume that these features existed prior to the acquisition of the blindspot syndrome. Otherwise one would have to expect at least some of these patients to show anomalous correspondence and suppression scotoma. While it is not possible to see what connection there could be between the blindspot and the other clinical features in these cases, I believe that these features are explained by assuming that the patients always had normal correspondence and little suppression. It is recognized that there are cases of esotropia with normal correspondence. For the establishment of anomalous correspondence, a number of factors are necessary. One such factor is a certain plasticity of the sensory apparatus of the eye. Some patients suppress more readily than others; some develop anomalous correspondence more readily than others. Both processes are closely connected. In general, patients with normal correspondence are more apt to complain of diplopia than patients with anomalous correspondence. Such patients would obviously be greatly benefited if they could keep their angle of squint within such limits that the image of the object of attention would always fall on the blindspot. Since suppression and anomalous correspondence go together, suppression scotomas are much more frequently found in anomalous than in normal correspondence. Also, they are larger the less stable the angle of squint is. The patient described by

Dr. Swan had, as he stresses, a stable angle of squint, and all the patients had normal correspondence. These factors, rather than the position of the blindspot, would seem to account for the absence of suppression scotomas. Dr. Swan has by definition excluded from his consideration patients in whom the blindspot forms part of a suppression scotoma. This may seem arbitrary, but these patients should, indeed, present a different behavior. I should like to ask Dr. Swan whether I am correct in assuming that the latter patients generally tended to have anomalous correspondence.

The selection which Dr. Swan has made also accounts for the ease with which diplopia is elicited by means of prisms in the patients with the blindspot syndrome. Dr. Swan emphasizes that diplopia can be elicited in the cases under discussion when the image of the fixation point is displaced from the blindspot in the deviated eye. He considers this a sure sign that the blindspot plays an essential part in alleviating the diplopia. If diplopia cannot be elicited in this way, he does not recognize the case as falling into the category of the blindspot syndrome.

In my experience, the cases of strabismus in which diplopia cannot be elicited by means of prisms are extremely rare. But it is much more difficult to do so in patients with anomalous than in patients with normal correspondence. It is to be expected that the patients included in Dr. Swan's group should readily report diplopia when the image of the fixation point is brought from the blindspot on an adjacent retinal area.

It is particularly difficult to correlate the last two common features of the cases, namely, the fair binocular cooperation, either from the start or after brief orthoptic treatment, and the amazingly good result with appropriate treatment, with the position of the blindspot. These features, too, seem to be inherent in the case and connected with the normal correspondence, rather than with the particular angle of squint.

The course of treatment suggested by Dr. Swan in these cases does not seem to be essentially different from that recommended in all cases of esotropia, but the results achieved are certainly far superior to those in the general run of cases. I should like to ask Dr. Swan whether he could quote for us comparative figures from his large experience with cases of esotropia of all types.

After studying the evidence which Dr. Swan has so ably presented to us, there still remains in my mind the question of the actual functional significance of the blindspot in cases of this condition. There is no doubt about the role of the blindspot in alleviating the diplopia when the angle of squint is such that the blindspot overlies the object of regard. But the other features of the cases are not explained by this position of the blindspot, and therefore I do not believe that one should give it such prominence as to speak of a "blindspot syndrome." It would seem to me better to state that Dr. Swan has selected a group of esotropic patients with normal correspondence, fair binocular cooperation and an excellent prognosis in whom the angle of squint is such that they are enabled to make use of the blindspot provided by nature to rid themselves of diplopia.

DR. KENNETH C. SWAN, Portland, Ore.: I am delighted with the discussion, for Dr. Adler and Dr. Burian have not only brought up some of the problems which my colleagues and I have considered but have introduced fresh aspects of the question.



I agree with Dr. Adler that the blindspot syndrome is usually associated with the so-called accommodational types of squint when it develops spontaneously. I appreciate his endorsement of our statement that inadequate treatment is of no avail.

I cannot state the average age of our patients, but the oldest patient in whom we have observed the syndrome is now 47. Determination of the youngest patient to develop the condition is limited not by the actual onset of the syndrome but by one's inability to recognize it; one cannot be certain of the diagnosis without subjective tests. We have been able to make these tests on some intelligent children 3 or 4 years of age.

Dr. Burian suggested several interesting points in the relation of normal correspondence to the presence of the blindspot in the central position. He also raised the question of the role of the blindspot in other conditions. During the eight year period in which we have been studying these cases, we have extended investigation of the field of binocular vision into other types of cases than those presented but have found it a field so large as to be beyond the scope of a single group of investigators. I make the plea that the study of the field of binocular vision be used in the routine examination of patients with esotropia. It is a visual test which is of great clinical importance, both in prognosis and in treatment; yet it is little used. It is simple to study the field of binocular vision of an intelligent youngster with the Lancaster red-green test or with similar filter-twin projector systems.

With respect to our good results, there should be some explanation. We have been persistent in treatment of these patients, and we have followed the results of treatment with the thoroughness required of a research problem. The average period of treatment for the cured patients was seventeen months, and the paper in no way reflects the extensive efforts expended in the training and observation of these patients by the orthoptic technicians and our staff.

Dr. Burian has made a good point in questioning whether the blindspot syndrome is a clearcut entity. We have designated the condition in this series of cases by this name primarily for the purpose of calling the attention of other ophthalmologists to the mechanism for purposes of study; however, it occurred to me, after hearing Dr. Burian's excellent discussion, that we should perhaps speak of "the blindspot mechanism," rather than limit ourselves to a single group of cases by using the term "the blindspot syndrome."

# USE OF ROENTGEN THERAPY FOR RETINAL DISEASES CHARACTERIZED BY NEW-FORMED BLOOD VESSELS (Eales's Disease; Retinitis Proliferans)

A Preliminary Report

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AND

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**D**URING the past eighteen months we have given intensive roentgen therapy to the posterior ocular segment in a series of patients with ocular diseases characterized by retinal and vitreous hemorrhages, with secondary fibrous tissue formation and with new-formed blood vessels extending into the vitreous. A total of 22 eyes in 14 patients have been so treated. The ocular disease was classified as typical Eales's disease in 8 of these patients, as atypical Eales's disease in 4 patients and as diabetic retinitis proliferans in 2 patients. The roentgen therapy has given sufficiently encouraging immediate results to warrant a preliminary report.

## TECHNIC OF ROENTGEN THERAPY

The irradiation technic devised by Martin and Reese<sup>1</sup> for the treatment of retinoblastoma was utilized to give large doses of roentgen radiation to the posterior ocular segment with minimal effects on the vulnerable anterior segment. The cones and portals employed were

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Read at the Fifty-First Annual Meeting of the American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology, Chicago, Oct. 16, 1946.

From the Wilmer Ophthalmological Institute of the Johns Hopkins Medical School, Baltimore, and the Institute of Ophthalmology of the Presbyterian Hospital and the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York.

1. Martin, H. E., and Reese, A. B.: Treatment of Retinal Gliomas by the Fractionated or Divided Dose Principle of Roentgen Radiation, *Arch. Ophth.* **16**: 733-761 (Nov.) 1936; Treatment of Retinoblastoma (Retinal Glioma) Surgically and by Irradiation, *ibid.* **27**:40-72 (Jan.) 1942; Treatment of Bilateral Retinoblastoma (Retinal Glioma) Surgically and by Irradiation, *ibid.* **33**:429-439 (June) 1945.

the same as those used in the cases of retinoblastoma (cylinders 2.5 cm. in diameter, shaped to fit the lateral orbital margin and the base of the nose). The following factors were employed: 250 kilovolts; filter, 1.5 mm. copper; half-value layer, 1.9 mm. copper; target-skin distance, 60 cm.; 30 milliamperes; portal size, 2.5 cm. The dosage was varied considerably, inasmuch as the exact nature of the diseases and the response to high voltage roentgen therapy were not known. The first patients treated received 400 r (in air) three times a week, the temporal portal being utilized more frequently than the nasal. The nasal portal was later eliminated because the presence of the fellow eye hinders its proper application, whereas in the cases of retinoblastoma the fellow eye has always been enucleated. Also, if the nasal portals are used for treatment of both eyes, the cross fire through the bridge of the nose gives a double dose to this area, which might produce necrosis. In the original cases 8,000 to 10,000 r was given through the temporal portal and 5,000 to 6,000 r through the nasal one, but in the later cases this was reduced to a total of 3,500 to 6,000 r, given only through the temporal portal. Erythema of the skin appeared after approximately 1,000 to 1,500 r had been given to a field and became brisker as the dose went higher. No ulceration or serious complications have arisen. The skin healed rapidly after treatment was discontinued, but late changes due to radiation (some atrophy and pigmentation of the skin) occurred in some patients. If the total dose did not exceed 6,000 r, the patients could tolerate 500 r three times a week through the temporal portal alone, thus shortening the treatment time. The eyes of all patients treated were examined before and at frequent intervals during and after the radiation therapy.

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## PLATE I

Fig. 1 (case 1; Nov. 28, 1944).—Right eye four months preceding roentgen therapy.

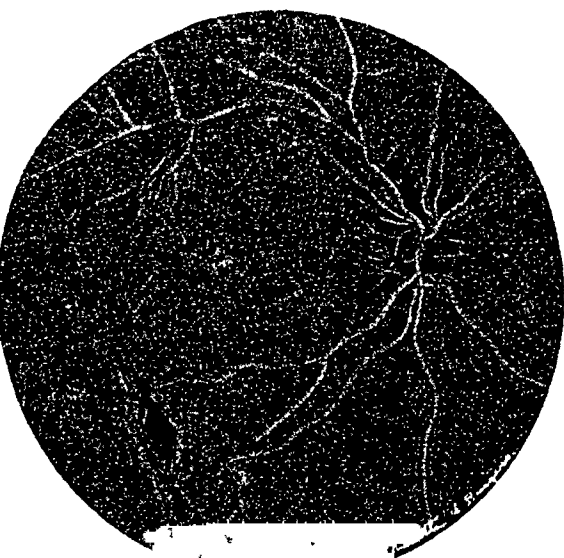
Fig. 2 (case 1; March 20, 1945).—Right eye shortly before roentgen therapy, showing extension of vessels into anterior vitreous.

Fig. 3 (case 1; May 25, 1945).—Right eye after receiving 8,000 r, showing marked regression of vessels.

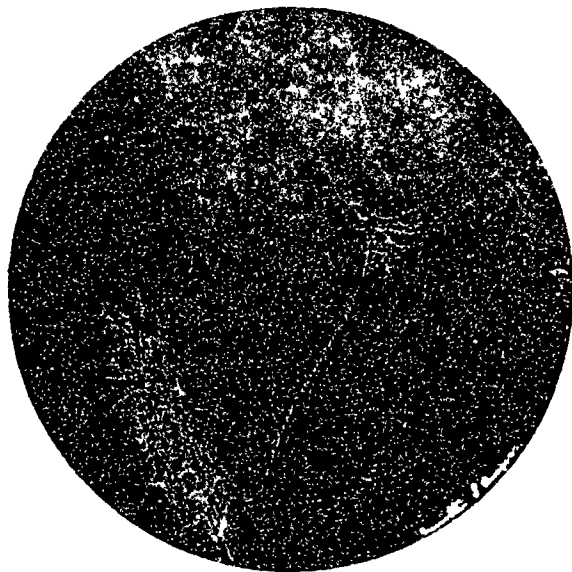
Fig. 4 (case 1; July 13, 1945).—Right eye after receiving entire course of 13,000 r, showing complete disappearance of new-formed vessels.

Fig. 5 (case 1; March 20, 1945).—Left eye two months preceding roentgen therapy.

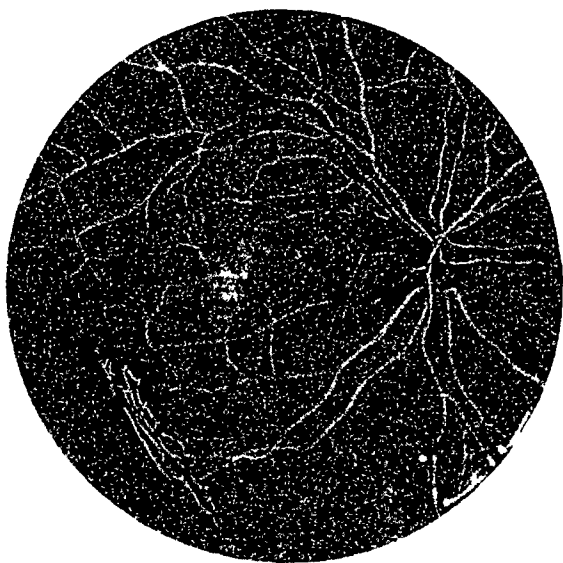
Fig. 6 (case 1; May 25, 1945).—Left eye immediately preceding roentgen therapy, showing extension of vessels into anterior vitreous.



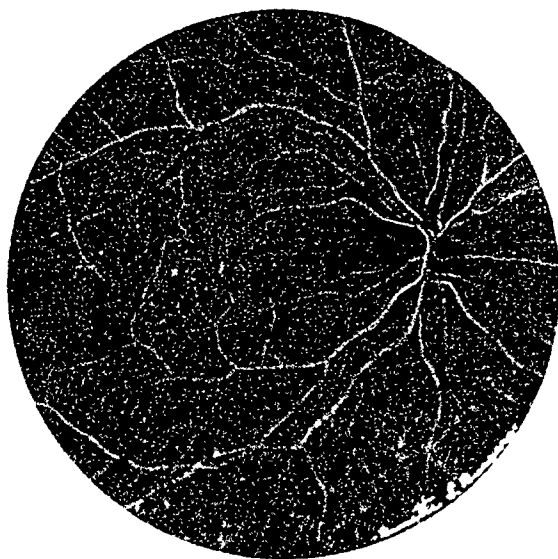
*Fig. 1*



*Fig. 2*



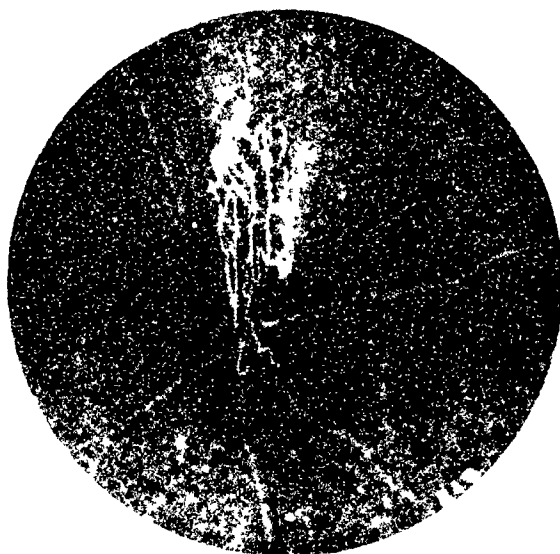
*Fig. 3*



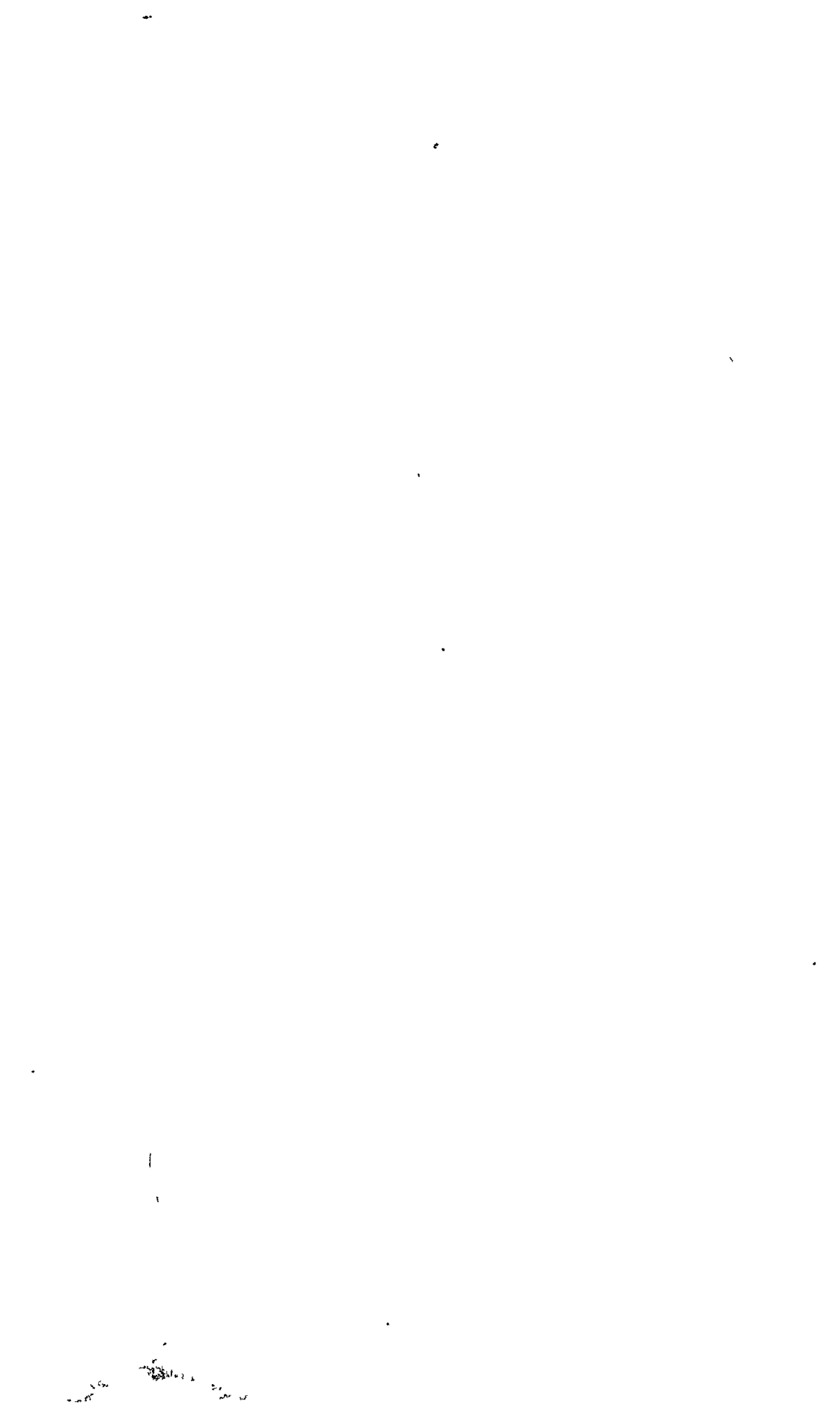
*Fig. 4*



*Fig. 5*



*Fig. 6*



## REPORT OF CASES

The 14 cases in this series are summarized in the accompanying table. Certain aspects of these cases are also described briefly.

## TYPICAL EALES'S DISEASE

CASE 1.—W. G., a white man aged 37, had a number of small recurrent hemorrhages with rapid proliferation of blood vessels in the vitreous of each eye. There was no apparent uveitis. During four months' observation without roentgen therapy, there were additional fresh hemorrhages in each eye with extension of new-formed vessels into the anterior portion of the vitreous, and at least one of the fresh hemorrhages in the vitreous of the right eye appeared to come directly from one of these new vessels. There was a questionable relationship of several of these recurrent hemorrhages to injections of tuberculin. The right eye was then treated with roentgen radiation (total dose, 13,000 r). There were no further vitreous hemorrhages in this eye, and the new-formed vessels disappeared with amazing rapidity (plate I, figs. 1 to 4). In the untreated (left) eye there were four additional recurrent hemorrhages and considerable progression of new-formed vessels during the succeeding two months. We no longer felt justified in withholding roentgen irradiation to the left eye, and the effect of therapy (total dose, 14,000 r) was similar to that in the right eye (plate I, figs. 5 and 6, and plate II, fig. 7). Subsequently, a patch of healed choroiditis could be seen in the far lower periphery of the left eye, but there was no definite choroiditis in the right eye. There has been no recurrence of either hemorrhages or formation of new vessels in the eighteen months since the eyes were treated. The patient was sensitive to 0.001 mg. of old tuberculin given intracutaneously.

CASE 2.—In B. deE., a white man aged 40, anterior uveitis developed in both eyes in March 1944. The uveitis subsided within several weeks, but massive vitreous hemorrhages developed in the right eye in August 1944 and in the left eye in February 1945. On July 3, 1945, he was found to have extensive retinitis proliferans with an abundance of new-formed vessels and partial retinal detachment in the right eye. In the left eye there was only a faint red reflex. Roentgen therapy was given both eyes (total doses, 12,000 r for the right eye and 10,000 r for the left eye). The new-formed vessels in the vitreous of the right eye thereupon disappeared completely, and there was considerable regression of the fibrous bands extending into the vitreous and of the retinal detachment. The left fundus still could not be seen when last examined (Sept. 15, 1946). The patient was sensitive to 0.001 mg. of old tuberculin given intracutaneously.

CASE 3.—S. M., a white woman aged 24, had recurrent retinal and vitreous hemorrhages for two years before she was first examined, on Jan. 6, 1944. Glaucoma had developed in the right eye ten days previously, with new-formed vessels on the anterior surface of the iris. This eye was enucleated, and examination showed in the posterior segment retinal and vitreous hemorrhages with fibrous tissue and new-formed vessels extending from the retina into the vitreous (fig. 8). The vitreous contained serous exudate, as well as actual hemorrhage. There were an inflammatory occlusion of the retinal veins and arteries and a peculiar thickening of the internal limiting membrane, but the inflammatory response was nonspecific (fig. 9). The left eye showed considerable fibrous tissue and new vessel formation extending into the vitreous and extreme retinal perivascular sheathing. Vision in her left eye gradually failed until June 1945, when she was given roentgen radiation, in a total dose of 15,000 r, to that eye. The new

*Data on Fourteen Patients Treated with Roentgen Radiation for*

Diagnostic Classification	Case No.	Age, Yr.	Sex	Eye	Vision with Correction*	Condition Preceding Roentgen Therapy				
						Duration of Symptoms	History of Vitreous Hemorrhages	New-Formed Vessels in Vitreous	Fibrosis Extending Into Vitreous	Retinal Detachment
Typical Eales's disease.....	1	37	M	R	20/15 -1	10 mo.	6 small	++++	±	-
				L	20/15 -2	12 mo.	13 small	++++	±	-
	2	40	M	R	20/70	11 mo.	1 massive; ? others	+++	+++	++
				L	1/200	6 mo.	1 massive; ? others	Faint	Red reflex	
	3	24	F	R	NLP	2 yr.	Several small	++++	+++	+
				L	20/100 +1	2 yr.	Several small	++++	+++	+
	4	30	M	R	20/20 -3	5 yr.	2 moderate	+++	++	-
				L	LP	5 yr.	1 small and 1 massive	-	Red reflex	
	5	29	M	R	3/200	7 mo.	Many small	+++	++++	+
				L	20/15	5 mo.	Many small	++	+	-
	6	26	M	R	20/400	17 mo.	Many moderate	?	++	++
				L	20/200	20 mo.	Many moderate	?	++	++
Atypical Eales's disease.....	7	37	F	R	20/70	1½ mo.	Many small	+++	+++	++
				L	1/200	5 mo.	Many small	+++	++++	++++
	8	46	M	R	HM	2 yr.	10+ small	?	++++	?
				L	HM	6 yr.	20+ small	?	++++	?
	9	25	F	R	20/100	1 mo.	Questionable	+++	+++	-
				L	20/15	....	0	-	-	-
	10	40	M	R	20/15	5 yr.	2 medium	+	+	-
				L	5/200	...	0	-	-	-
	11	42	M	R	20/70 +1	6 mo.	10 small	-	+	-
				L	20/20 -1	14 mo.	20 small	-	-	-
	12	34	F	R	NLP	9 yr.	Many	-	Red reflex	
				L	LP	9 yr.	Many	±	+	±
Diabetic retinitis proliferans.....	13	53	F	R	20/40	3 yr.	Questionable	++	++	-
				L	20/40	3 yr.	0	-	-	-
	14	42	M	R	20/200	1 yr.	Questionable	++	±	-
				L	20/200	1 yr.	Questionable	+++	+++	-

\* NLP indicates no light projection; LP, light projection, and HM, hand movements.





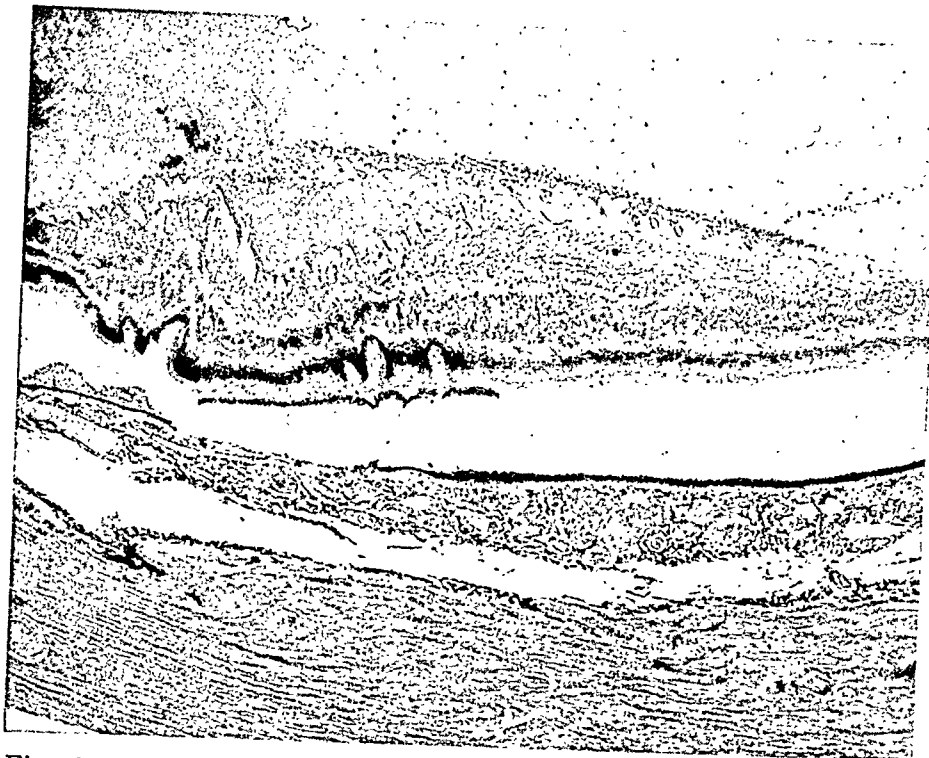


Fig. 8 (case 3).—Photomicrograph from posterior segment of right eye, showing new-formed vessels and fibrous tissue extending from retina into vitreous hemorrhage.

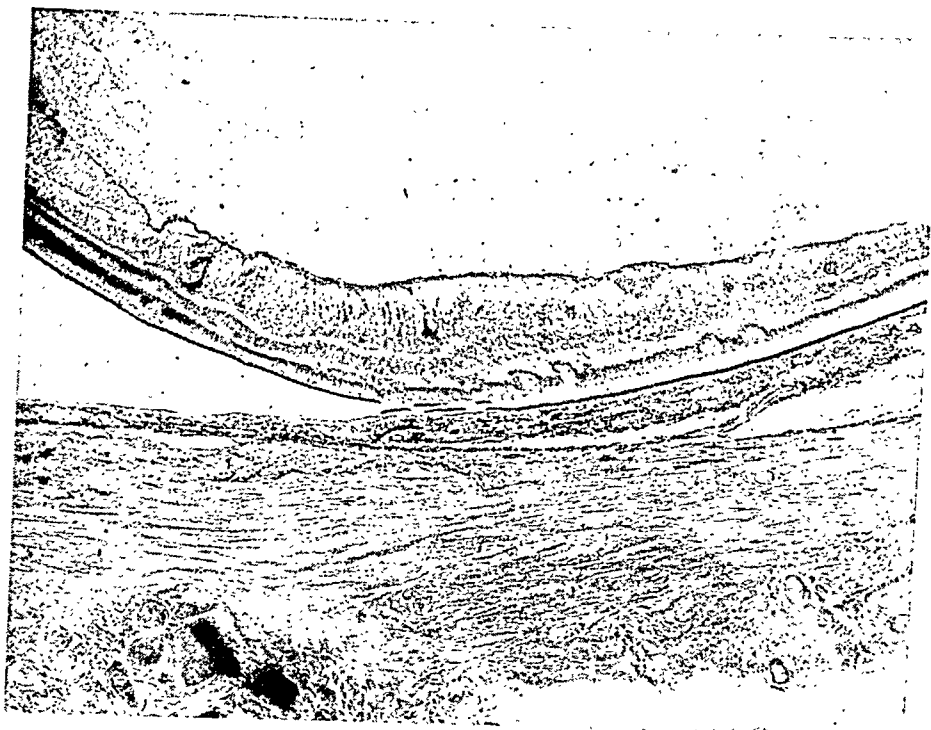


Fig. 9 (case 3).—Photomicrograph from posterior segment of right eye, showing retinal perivascular inflammation, inflammatory occlusion of retinal veins and peculiar thickening of internal limiting membrane.

vessels disappeared, and there have been no fresh hemorrhages during the fourteen months she has been followed since the irradiation; but there are still many fine dilatations and tortuosities of the retinal venules, and the perivascular streaking is unchanged. There was never any apparent uveitis in either eye. A patch test gave a negative reaction to a 1:10,000 dilution of old tuberculin U. S. P. At one time she had eosinophilia, with a count of from 6 to 8 per cent eosinophils, and a 2 plus reaction to the cephalin flocculation test; but all other examinations, including determination of the sedimentation rate, complete blood studies and muscle biopsy, gave normal results.

CASE 4.—P. M., a white man aged 30, had a history of at least two distinct vitreous hemorrhages in each eye during the preceding five years. Examination (Aug. 10, 1945) of the right eye showed a little blood scattered through the lower part of the vitreous, with new-formed vessels extending far into the vitreous in three areas and small aneurysmal dilatations in the new vessels in the lower temporal part of the vitreous (plate II, fig. 10). There was a small, apparently fresh vitreous hemorrhage, which appeared to come from one of the new-formed vessels in the anterior portion of the vitreous (not shown in the illustration). The left eye had poor light projection and no red reflex. The right eye was given roentgen therapy (total dose, 15,000 r). The new-formed vessels disappeared completely, but a few tiny aneurysmal dilatations of retinal venules remained in the lower temporal quadrant of the retina (plate II, fig. 11). There has been no recurrence of hemorrhages or of formation of vessels during the year since he was treated. There was never any apparent uveitis in either eye. The patient was sensitive to 0.001 mg. of old tuberculin U. S. P. given intracutaneously, and biopsy of a cervical lymph node showed actual tubercle bacilli.

CASE 5.—R. B., a white man aged 29, began to have many small recurrent retinal and vitreous hemorrhages in the right eye during July 1945, and in the left eye two months later. Examination on Feb. 13, 1946 showed extensive fibrosis and new vessel formation in the vitreous of the right eye, with partial retinal detachment. In the left eye there were scattered hemorrhages in the temporal part of the retina and the vitreous, with aneurysmal dilatations of some retinal venules in this area, an area of retinal hemorrhage with obliteration of a terminal arteriole in the nasal periphery and a sheet of new-formed vessels extending into the vitreous from the nasal side of the disk (fig. 12). There was no evidence whatever of any vitreous or retinal hemorrhage close to the area of retinitis proliferans, which extended forward from the disk. Roentgen therapy was given in a total dose of 3,500 r to the right eye and of 4,000 r to the left eye. There was partial collapse of the new-formed vessels in each eye, only the larger trunks remaining patent, but little or no decrease in fibrosis (fig. 13). On July 1, 1946, the patient had symptoms of another hemorrhage in the left eye and was found to have two small retinal hemorrhages with a faint diffuse haze in the vitreous (plate II, fig. 14). He was given an additional 2,000 r to the left eye, and has not been reexamined since the course was completed. The indistinct scar in the nasal periphery of the left eye was the only evidence of probable uveitis in either eye. He was sensitive to 0.001 mg. of old tuberculin, given intracutaneously.

CASE 6.—R. R., a white man aged 26, began having recurrent retinal and vitreous hemorrhages in both eyes eighteen months before he was examined, and six months before examination he was said to have shown "organization" of hemorrhages, with an area of chorioretinitis in the right eye but no uveitis in the left eye. He was said to have given a positive reaction to tuberculin (dilution

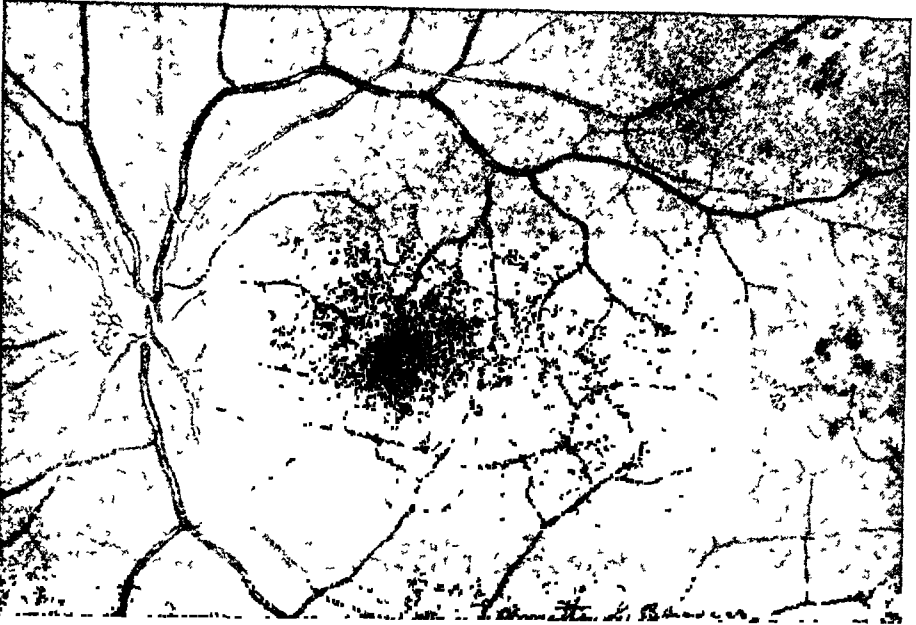


Fig. 12 (case 5; Feb 13, 1946)—Left eye immediately preceding roentgen therapy.

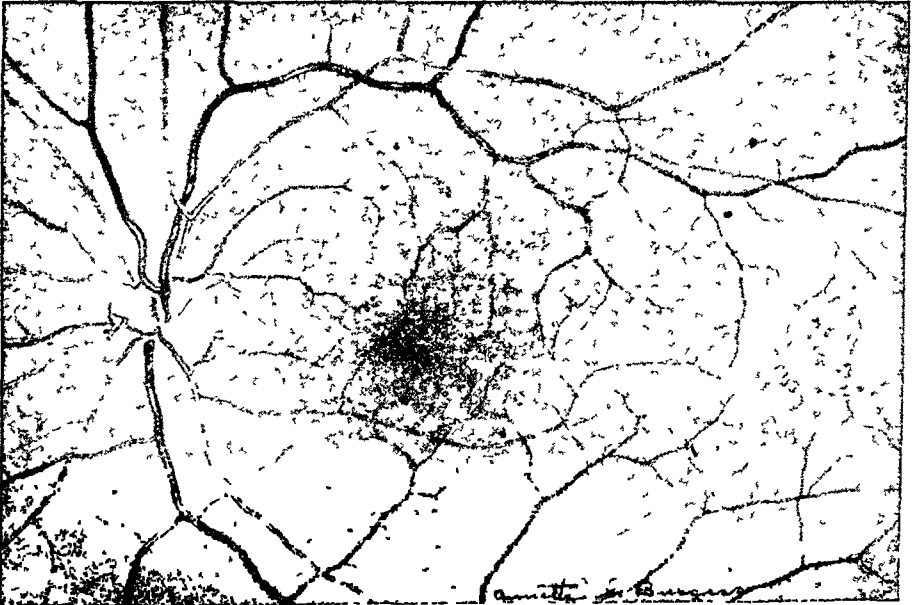


Fig. 13 (case 5; June 5, 1946).—Left eye after conclusion of first course of therapy (4,000 r), showing partial collapse of new-formed vessels and persistence of aneurysmal dilatations of retinal venules in temporal periphery.

not known). On March 1, 1946, the vitreous of each eye contained so much blood that nothing could be determined ophthalmoscopically except that there was retinitis proliferans with partial retinal detachment in each eye. Roentgen therapy (4,000 r to each eye) was followed by gradual clearing of the vitreous in each eye. Three months later vision had improved from 20/200 to 20/25 in the left eye, and the fundus could be seen fairly well, showing partial retinal detachment still present, with moderate fibrosis on the surface of the retina but no new-formed vessels. The right fundus still could not be seen plainly.

CASE 7.—O. St. J., a white woman aged 37, had many small recurrent vitreous hemorrhages in her left eye during November 1945, and a similar hemorrhage in her right eye on Feb. 1, 1946. Examination March 15, 1946 showed small patches of blood in the vitreous of the right eye and extensive retinitis proliferans with many new-formed vessels and partial retinal detachment (fig. 15). The left eye showed a similar, but more advanced, picture, there being massive retinitis prolifer-

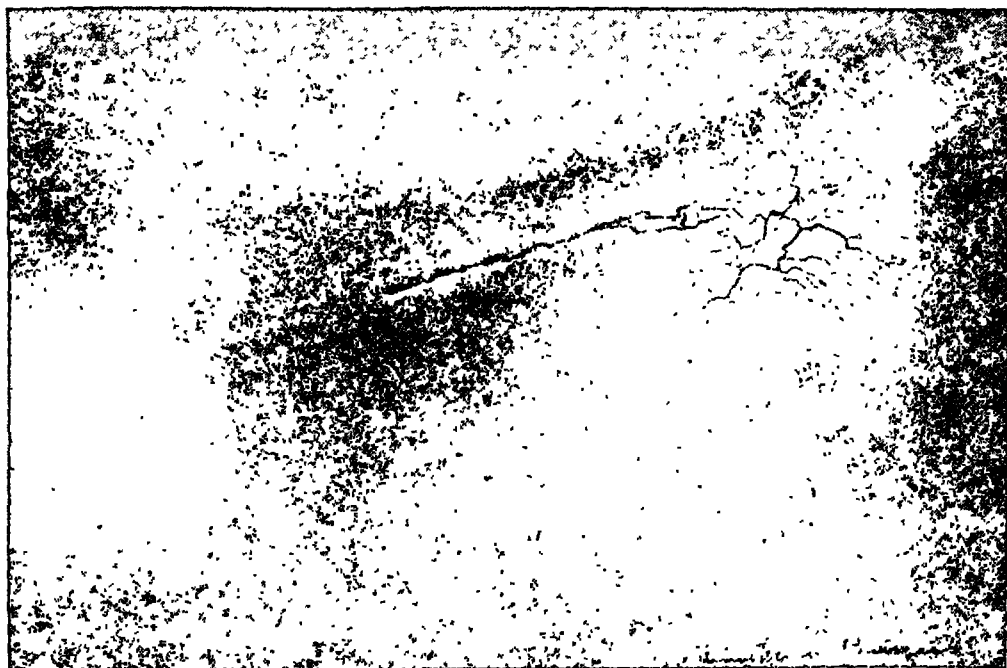


Fig. 15 (case 7; March 26, 1946).—Right eye immediately preceding roentgen therapy.

ans with complete retinal detachment. Roentgen therapy was given in a total dose of 4,000 r to each eye. The smaller new-formed vessels in both eyes completely disappeared but the larger ones only shrank in size, remaining patent (fig. 16). There were some decreases in fibrosis of the vitreous and some flattening of the right retina, but the left retina remained completely detached. There has been no recurrence of hemorrhages or of new vessel formation during the five months of observation since the roentgen therapy. There was never any apparent uveitis. The patient had a negative reaction to 1 mg. of old tuberculin given intracutaneously but showed involvement of the hilar nodes in roentgenograms of the chest.

CASE 8.—G. P., a white man aged 46, had had at least twenty vitreous hemorrhages in his left eye during the preceding six years and at least ten in his right eye during the preceding two years. Examination on July 10, 1946 showed considerable unabsorbed blood in each vitreous. Details of the fundus could not be

seen except that massive retinitis proliferans was dimly visible in each eye. Roentgen therapy was then given, 4,000 r to each eye. At the time of writing, the vitreous is slowly clearing in each eye, but details of the fundus are still not clearly visible. There has been no apparent uveitis. He has shown a positive reaction to 0.001 mg. of old tuberculin U. S. P. given intracutaneously and has a healed tuberculous lesion in the apex of his left lung.

#### ATYPICAL EALES'S DISEASE

CASE 9.—B. G., a white woman aged 25, had numerous retinal and questionable vitreous hemorrhages in her right eye in January 1946. Examination on Feb. 19, 1946 showed marked fibrosis with new vessel formation on the retina and extending slightly into the vitreous of that eye. There was apparent partial occlusion of several of the retinal veins. The left eye was normal except for unusually large veins. The patient received 4,000 r to the right eye, beginning April 13, 1946.



Fig. 16 (case 7; July 31, 1946).—Right eye three months after completion of therapy (4,000 r), showing partial collapse of new-formed vessels.

The new-formed vessels partially disappeared, and there have been no additional hemorrhages in the five months since the eye was treated. She had diabetes for eighteen months preceding therapy but no diabetic retinopathy. She had no apparent uveitis, and sensitivity to tuberculin was not determined.

CASE 10.—A. H., a white man aged 40, had a history of a massive retinal and vitreous hemorrhage in his right eye while lifting a heavy weight five years previously. The vitreous hemorrhage had cleared quickly, and a photograph of the fundus taken one month later (fig. 17) showed an extensive retinal hemorrhage along the lower branch of the superior temporal vein, occurring distal to a point where this vein coiled in corkscrew fashion around the superior temporal artery. The retinal hemorrhage had gradually cleared, with some fibrosis; and the patient had had no further symptoms until a second large hemorrhage occurred on Dec. 1, 1945, this time spontaneously. Examination on December 18 showed that the left eye was normal except for amblyopia ex anopsia. In the right eye there was a massive

retinal and a slight vitreous hemorrhage along the distribution of the lower branch of the superior temporal vein, a small branch of which was obliterated, with some organization of the hemorrhage (including new-formed vessels) in places. There was also white serous exudate in the lower portion of the vitreous. Throughout the involved area of the retina, but extending also into areas supplied by the lower temporal vein, there were corkscrew irregularities and tiny aneurysmal dilatations of the fine retinal venules (fig. 18). These small varicosities were still present after roentgen therapy (6,000 r) but were less pronounced than before treatment (fig. 19). There was slight decrease in fibrosis following roentgen therapy, and the new-formed vessels disappeared. He had symptoms of two small hemorrhages during June 1946, and examination on October 1 showed several tiny retinal hemorrhages and cotton-wool exudates scattered about the posterior portion of the fundus, partial absorption of the serous exudate in the lower part of the vitreous and a peculiar localized plexus of dilated capillaries at one point along the remaining branch of the originally involved vein (fig. 20). He is now receiving



Fig. 17 (case 10; February 1941).—Right eye one month after first hemorrhage, showing corkscrew anomaly in lower branch of superior temporal vein.

3,000 r of additional roentgen radiation. There was never any evidence of uveitis. He was sensitive to 0.001 mg. of old tuberculin U. S. P. given intracutaneously.

CASE 11.—L. P., a white man aged 42, had had numerous retinal and small vitreous hemorrhages in the left eye during the preceding fourteen months and in the right eye during the preceding six months. He had had subjective exacerbations in both eyes approximately forty-eight hours after each of three intracutaneous injections of tuberculin. Examination of the right eye on July 19, 1946 showed slight vitreous hemorrhage and a peripheral medium-sized retinal hemorrhage with early organization, with dilatation of a retinal vein just at the site of its emergence from the area of hemorrhage. In the left eye there were more vitreous hemorrhages and clumps of white serous exudate in the lower portion of the vitreous, with streaks of retinal hemorrhage undergoing absorption, but without organization, in the temporal periphery. A retinal vein supplying the latter area had two short stretches of doubling of the channel at one place, with a trace of adjacent absorbing retinal hemorrhage, suggesting occlusion and recanalization of the vein at this point. There was also a small aneurysmal dilatation at one

point in a branch of the superior nasal vein, but no adjacent hemorrhage. A total of 4,000 r was given each eye. The patient has not been examined since the conclusion of this therapy (Aug. 10, 1946).

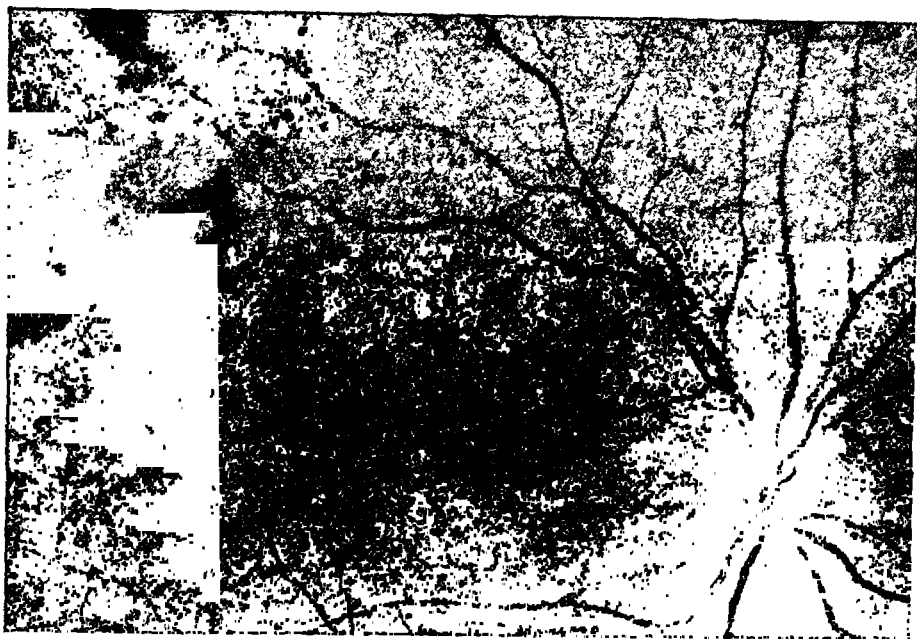


Fig. 18 (case 10; Dec. 18, 1945).—Right eye immediately preceding roentgen therapy. Note the varicosities and tiny aneurysmal dilatations in terminal venules of lower temporal vein, as well as of upper vein.

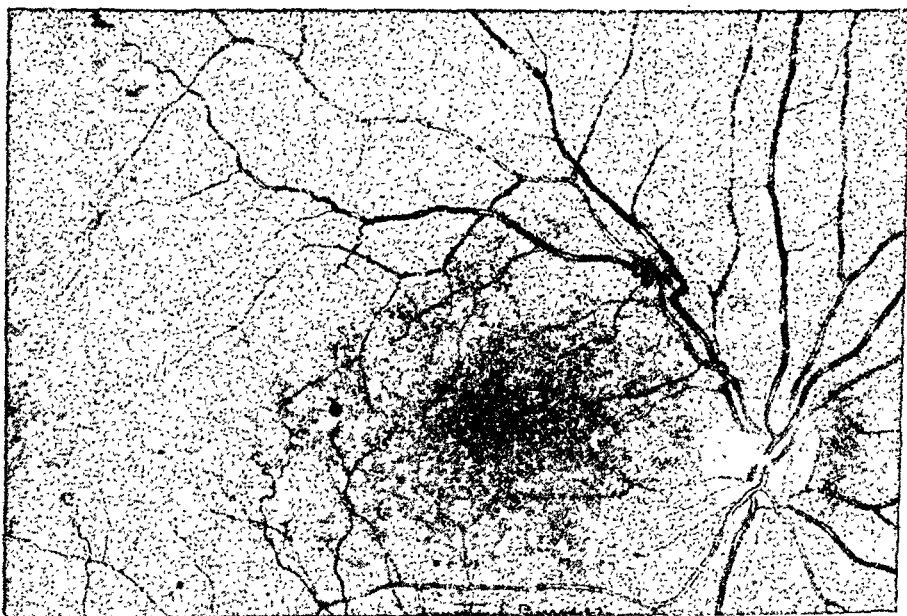


Fig. 19 (case 10; Feb. 12, 1946).—Right eye after completion of therapy (6,000 r), showing regression of new-formed vessels but some persistence of varicosities in retinal venules.

CASE 12.—S. A., a white woman aged 34, with a history of many hemorrhages in the vitreous of both eyes during the preceding six years, was first examined March

5, 1943. The right eye was blind, with evidence of healed anterior uveitis and a dense complicated cataract. The left eye showed a normal anterior segment, some vitreous hemorrhage and scattered retinal hemorrhages with fibrosis. Vision in the left eye was 20/70 at that time. During the next three years she had several recurrent vitreous hemorrhages in the left eye, and on June 9, 1946 there developed acute anterior uveitis with a large hypopyon (containing some hemorrhage) and temporary loss of light perception. The anterior uveitis cleared within a few days, and she was found to have moderate vitreous hemorrhage. Roentgen radiation (3,500 r) was given to the left eye. The vitreous hemorrhage gradually cleared within a month, and she was then seen to have indistinct white areas (apparently a mixture of atrophy and of fibrosis) scattered throughout the retina, with a pale disk and vision still limited to light perception. She had aphthous lesions of the mucous membranes, deficiency of plasma ascorbic acid, slightly increased capillary fragility, a probable tuberculous infection of one kidney and sensitivity to 0.001 mg. of old tuberculin given intracutaneously.

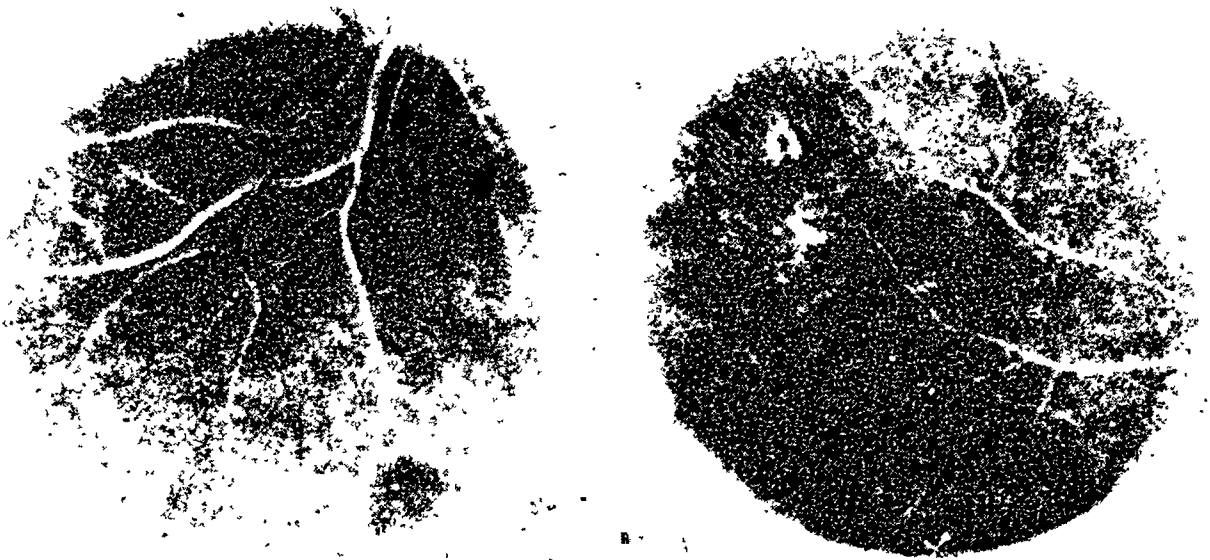


Fig. 20 (case 10).—Right eye seven months later, showing new retinal hemorrhages and cotton-wool exudates, and small plexus of dilated capillaries.

#### DIABETIC RETINITIS PROLIFERANS

CASE 13.—M. B., a Negro woman aged 53, was found to have diabetes in 1943. At that time, she had many small hemorrhages and irregular waxy exudates in each retina. In May 1945, new-formed vessels and fibrous tissue began growing into the vitreous of the right eye from the upper temporal portion of the retina and from the disk. The retinitis proliferans progressed, and on April 1, 1946 (fig. 21) roentgen therapy (4,000 r) was begun to the right eye. The new-formed vessels collapsed completely within seven weeks, and the fibrosis became slightly less (fig. 22). New retinal hemorrhages have since occurred from time to time, but there has been no recurrence of retinitis proliferans during the five months since roentgen therapy.

CASE 14.—I. W., a white man aged 42, had a history of diabetes of three years' duration and of blurred vision for nine months. Examination March 27,



1946 showed multiple retinal hemorrhages and hard, white exudates and considerable retinitis proliferans, including many new-formed vessels, in each eye. Roentgen therapy (4,000 r to each eye) resulted in marked diminution, but not complete



Fig. 21 (case 13; April 1, 1946).—Right eye immediately preceding roentgen therapy.



Fig. 22 (case 14; June 4, 1946).—Right eye after completion of therapy (4,000 r), showing disappearance of new-formed vessels.

collapse, of the new-formed vessels, with temporary improvement of vision. However, the patient returned five months later with fresh vitreous hemorrhages and greatly reduced vision in each eye.

## SUMMARY OF MATERIAL

The ocular diseases in these 14 patients did not constitute a single entity, but all the 22 eyes treated had in common retinal and vitreous hemorrhages with progressive formation of new vessels and fibrous tissue on the surface of the disk or retina and extending more or less into the vitreous. In every case the new-formed vessels and fibrosis could be called "retinitis proliferans," provided this term be used in a purely descriptive sense.

The ocular disease was classified as "typical" Eales's disease in 8 patients. This group consisted of 6 men and 2 women, all young, with bilateral recurrent retinal and vitreous hemorrhages of obscure origin and with retinitis proliferans. One patient had evidence of old healed bilateral anterior uveitis; 3 others had had probable unilateral choroiditis at some time before they were examined, and in a fifth patient an eye enucleated without having had roentgen therapy showed a nonspecific inflammatory occlusion of the retinal vessels. Reactions to tuberculin were positive in 6 of these 8 patients, 5 of them giving a positive reaction to the small dose of 0.001 mg. of old tuberculin U. S. P. injected intracutaneously and the sixth having shown a positive reaction to an unstated quantity given elsewhere. One of the patients in this group was insensitive to 1 mg. of old tuberculin given intracutaneously, but a roentgenogram of the chest showed enlarged hilar nodes. The final patient did not react to a patch test with a 1:10,000 dilution of old tuberculin, and the test was not carried further. These patients represented various occupations—business man, lawyer, seaman, clerk, housewife and army officer.

The ocular disease was classified as "atypical" Eales's disease in 4 patients. In 1 of these patients the only affected eye showed probable partial occlusion of several retinal veins, which may have initiated the process. A second patient had hemorrhages recurring at first only in a localized area of the only involved eye and showed an anomalous, sharply localized narrowing of the retinal vein supplying this area. A third patient, with bilateral involvement, showed two localized dilations of retinal veins and probable localized occlusion and recanalization of another small vein. The fourth patient had classic aphthous uveitis.

The ocular disease was classified as diabetic retinitis proliferans in 2 patients. Both patients had long-standing diabetes with bilateral diabetic retinopathy, including retinal hemorrhages and exudates but little evidence of hemorrhages in the vitreous except for a faint haze. Typical retinitis proliferans had developed in the 3 eyes which were treated.

## SUMMARY OF RESULTS

The first, and most striking, effect of roentgen therapy was a diminution in the new-formed vessels. The smaller vessels began shrinking within two to three weeks after therapy was begun and invariably disappeared from ophthalmoscopic visibility within four to eight weeks, even if the total dose was only 3,500 r. If a dose of not more than 4,000 r was given, the larger new-formed vessels usually showed some shrinkage in caliber but remained patent indefinitely. However, in the 6 eyes which received a total dose of 10,000 r or more, even the largest new vessels completely disappeared from ophthalmoscopic visibility. There has as yet been no definite recurrence of new-formed vessels in any of the 22 eyes treated.

Regression of fibrosis was less striking than the regression of vessels. If the fibrosis was scanty, almost translucent, before therapy began and if 10,000 r or more was given, the regression of fibrous tissue was marked. However, dense fibrosis, of long duration, was reduced only slightly or moderately even with heavy dosage, and doses of only 4,000 r had little effect, even on scanty fibrosis.

The tiny dilatations of retinal venules in 2 cases appeared to be less prominent but were still present after large doses of roentgen radiation, and the varicosities of the tiny retinal venules showed no perceptible change.

In the group of 8 patients with "typical" Eales's disease there has been only one recurrent hemorrhage. It consisted of two small retinal hemorrhages and a faint vitreous haze in an eye which had received only 4,000 r and did not show complete collapse of the larger new-formed vessels. This cessation of recurrent hemorrhages appeared to be more than a coincidence in 3 of these patients, in whom many small vitreous hemorrhages had appeared in each eye at intervals of one to four weeks, right up to the beginning of therapy. However, this cessation of hemorrhages may well have been the result of the breaking up of a "vicious cycle" (see "Comment"), rather than an effect on factors initially responsible for the ocular diseases. It must be emphasized that these results are only immediate, short term results, since only 4 patients have been followed longer than ten months. As we do not know the primary cause of the retinal and vitreous hemorrhages, we cannot report at present on the effects of the treatment in this regard, nor can we yet determine the permanency of the immediate effects.

In the group of 4 patients with "atypical" Eales's disease, there has as yet been a recurrent hemorrhage only in the patient with an anomalous localized constriction of a retinal vein. However, there has not yet been an appreciable follow-up period for the other 3 patients.

In the 2 patients with diabetic retinitis proliferans, fresh retinal hemorrhages have continued to appear, and in 1 patient fresh vitreous hemorrhages developed five months after therapy, even though the new-formed vessels were markedly diminished. It seems unlikely that roentgen therapy could result in permanent benefit for patients in this category until an effective treatment for diabetic retinopathy itself has been discovered.

#### COMMENT

Most retinal and vitreous hemorrhages gradually absorb without inducing retinitis proliferans, but sometimes, especially with recurrent hemorrhages, there is proliferation of new vessels and of fibrous tissue on the surface of the retina or disk and into the vitreous. Regardless of the primary cause of the hemorrhages, it is probable that this stimulation of new tissue formation is often a direct result of some factor of blood in the vitreous, although the components of blood which may be responsible for such a proliferative reaction are not known.

Small peripheral vitreous hemorrhages may result in retinitis proliferans arising from the disk, even though no blood pigment is visible in the vitreous around the disk. Further, retinitis proliferans may result from diabetic retinopathy, and progression into the vitreous may continue even when no actual blood cells are visible in the vitreous. These observations suggest the possibility that some factor in blood serum alone may stimulate such proliferation, although the presence of hemolyzed cells not visible ophthalmoscopically cannot be ruled out in such conditions.

The new-formed vessels extending into the vitreous have very thin walls and histologically are surrounded by a zone of homogeneous transudate and delicate sheets of fibroblasts. The thin walls of these vessels can certainly break, with actual seepage of blood into the vitreous, as we have observed in 2 cases. Also, it is theoretically possible that a transudate of serum from the thin-walled, new-formed vessels themselves may account for continued proliferation of new vessels even after the primary retinal and vitreous hemorrhages have cleared. Thus, in certain instances a vicious cycle may be established, the new, thin-walled vessels in the vitreous stimulating their own progression by actual hemorrhage, or possibly by simple transudation of serum. Our use of roentgen therapy has been directed primarily toward the destruction of new-formed vessels in the vitreous. If the vicious cycle just described plays as large a role in progressive retinitis proliferans as we believe, the results of roentgen therapy may prove to be permanent in those cases in which the primary cause of the hemorrhages is self limited, rather than of indefinite duration. This happy result cannot be hoped for in cases of diabetes but may be in many cases of Eales's disease.

The varicosities and tiny dilatations in retinal venules described in 3 of these cases all occurred in areas where retinal hemorrhages had been absorbed. For many years these vascular changes have been known to result at times from retinal hemorrhage and to remain permanently after absorption of the hemorrhage. It seems unlikely that they induce more hemorrhages or retinitis proliferans. The vessels are not newly formed, and they show little, if any, shrinkage as a result of even massive roentgen therapy.

We have purposely avoided the clinical terms periphlebitis and periarteritis because, while these terms denote actual inflammation around vessels, they are commonly used to indicate perivascular streaking. As a matter of fact, perivascular streaking is not necessarily indicative of an inflammatory process, but represents merely a sequela of absorption of large retinal hemorrhages in the areas supplied by the vessels.

A discussion of the etiologic factors in Eales's disease is outside the scope of this paper. Eales's disease may (reportedly) be caused by tuberculosis, glandular disturbance (such as menstruation), thromboangiitis obliterans, hemophilia, capillary fragility, thrombopenic purpura, ocular hypotony, low blood calcium, high blood pressure, low blood pressure and foci of infection. We suggest a primary vascular neoplasia, such as atypical angiomas retinae, as another cause—certainly, the end results are pathologically similar. In any event, we are unable even to give a concise definition of Eales's disease, let alone evaluate the primary causes and explain the facts that 80 per cent of the cases are of males and that the disease is usually bilateral.

#### SUMMARY

Intensive roentgen therapy to the posterior ocular segment was given during the eighteen months prior to this report in a series of patients with ocular diseases characterized by retinal and vitreous hemorrhages and by new-formed blood vessels and fibrous tissue extending from the retina or disk into the vitreous (retinitis proliferans).

A total of 22 eyes in 14 patients were treated. The ocular diseases were classified as typical Eales's disease, in 8 patients; atypical Eales's disease, in 4 patients, and diabetic retinitis proliferans, in 2 patients.

The irradiation technic devised by Martin and Reese for the treatment of retinoblastoma was utilized to avoid damage to the anterior ocular segment. A total dose of 3,500 to 15,000 r was given each eye treated. Doses of approximately 6,000 r are probably optimal.

Depending on the dose of roentgen radiation given, there were moderate to complete collapse of new-formed vessels and variable regression of fibrosis. There has been only one recurrent hemorrhage following treatment in the 8 cases of typical Eales's disease, an effect which has appeared to be of immediate significance, but the perma-

nency of these immediate results is not established because sufficient time has not elapsed since the patients were treated. In the 2 patients with diabetic retinitis proliferans, hemorrhages have continued to appear since treatment, and permanent beneficial results can hardly be expected.

Wilmer Ophthalmological Institute, Baltimore (Dr. Guyton).

Institute of Ophthalmology of Presbyterian Hospital (Dr. Reese).

## DISCUSSION

DR. MOACYR E. ALVARO, São Paulo, Brazil: The roentgen treatment of hemorrhagic alterations of the retina dates back to the end of the second decade of this century; curiously, it was through analogy with the good results obtained in the treatment of hemorrhages in cases of myoma uteri that Hessberg, in 1919, tried the roentgen treatment for hemorrhagic glaucoma. In the following years roentgen irradiation for hemorrhagic conditions of the fundus has met with increasing favor. However, there appears still to be considerable difference of opinion regarding the results. A substantial group, comprising the great majority of those who have reported cases of retinal hemorrhages treated with roentgen radiation, seems to approve of the method and advocates the use of small doses, totaling 600 r, or even less. Thus, Basile, Saul, Zingale, Loewenstein, Reise, Schmerer, Hessberg, di Marzio, Jendralski and others have reported good results. Another group, however, is less enthusiastic. Cordes favored roentgen therapy only for tuberculous periphlebitis in young persons and discouraged it for vascular occlusion due to sclerosis. Schnyder and Foster cautioned against producing inflammatory conditions, which, in turn, might cause retinal detachment. Von Grósz warned of the possibility of hemorrhages due to roentgen radiation, and Stock, Mylius and Lorey reported cases in which this actually happened; in these cases, however, larger doses had invariably been given.

According to the general consensus, the action of the roentgen rays is always bionegative. The so-called stimulating action is apparently indirect, through catabolic substances produced by the primary destructive action of the rays on the tissues, through changes in the globulin-albumin ratio and through changes in the  $p_H$ .

An electron can be depicted as a small bullet 1 mm. in diameter revolving in a sphere—the atom—about 50 to 100 meters in diameter; the protein molecule has from 800 to 1,500 atoms, and a cell from 1,000,000 to 100,000,000,000 molecules. The impact of one of those electrons on the minute part of a cell which stops it (absorbs the rays) may cause several reactions. According to Dessauer, it produces heat, which coagulates some of the albumin of the cell. According to others, it produces changes in the electric charge of the colloids. Be it one or the other, or still some other phenomenon, the fact remains that there will always be changes as the result of the impact—changes in the ion concentration of mineral salts, in the cholesterol contents, in the viscosity of the plasma and in the permeability of cellular membranes.

Sensitivity to roentgen rays varies considerably from cell to cell in the different biologic species, and even in the same species, according to the type of cell. The more differentiated the cell, the less sensitive

it is. The action is always directly proportional to the activity of the cell, newly formed tissue being always more receptive.

White blood cells, having nuclei, are more sensitive to roentgen radiation than are red blood cells, except *in vitro*. Lymphocytes are the most sensitive of all, the sensitivity decreasing in the following order: monocytes, eosinophils, myelocytes and neutrophils.

The effect of roentgen rays on the blood vessels varies with the amount of radiation used. In the retinal blood vessels histologically studied by Hoffmann in enucleated eyes which had been given large doses of roentgen radiation in treatment of malignant tumors, there appeared to be considerable dilatation of both arteries and veins, with changes in the endothelial cells, where the nuclei showed pronounced tumefaction; moreover, there could be seen fibroblasts in great numbers, as in intense proliferation of the intima, and even consequent closing of the lumen of the vessels. When smaller doses are used, there is immediate dilatation of the capillaries, as proved by David and Gabriel in their experiments. In order to explain the vasodilatation, several theories have been proposed. 1. According to Best, Date and Dudley, roentgen rays are able to liberate histidine and similar substances from the tissues. Histidine is then transformed into histamine, which, in turn, once in the circulating blood, causes the capillaries to dilate. 2. According to Ellinger, roentgen radiation acts directly on the nuclei of the endothelial cells, which appear to be very sensitive to these rays. This action would explain the changes observed in the intima, even in larger blood vessels. 3. According to the investigations of Sunder Plassmann, nerve terminations, in contrast to other nerve tissue, are very sensitive to roentgen rays. In his experiments he was able to show that the nerve terminations, which normally form a reticulum, after small doses of roentgen radiation had the appearance of a conglomerate mass. Thus, the roentgen rays would influence directly the terminal vasomotor branches, as has been shown by Jungenburg and Schlepakow in roentgen treatment of the thyroid gland. There is no reason that the roentgen rays could not have the same effect on the terminations of the vasomotor nerves in the vessels of the retina. Even with small doses, there seems always to be an increase in permeability of the endothelium of the capillaries, enabling a more active exchange of fluids between the circulating blood and the adjacent tissues.

What happens in the retina when hemorrhages occur? The blood flowing out of the blood vessels will be found to spread superficially among the nerve fibers, the hemorrhage then having the form of a candle flame; or it will penetrate more deeply between the fibers and take on a globular form, or it will break through the internal limiting membrane and into the vitreous. These hemorrhages can be rapidly resorbed without leaving any residue; but, more often than not, especially if they recur, degenerative changes may appear, and deposits of substances arising from disintegration of nerve cells, such as cholesterol and other lipids, may be found, as in glial or conjunctival proliferation. The time in which a hemorrhage will be completely resorbed varies from four days to weeks, months, or even years. In general, the larger the hemorrhage, the longer it will take to disappear; and the longer the disintegrating blood cells stay in direct contact with the adjacent nerve cells of the retina, the more harmful it is for the latter.

When the retinal hemorrhage is due to a stoppage in the blood flow, whether it be in an artery or in a vein, a certain portion of the retina, dependent for its nourishment on the impaired vessel, will deteriorate. In the case of arterial stoppage, the circulation of the blood may be reinstated through an existing anastomosis, as in the coexistence of the two systems—central artery and cilioretinal artery—or through new-formed blood vessels, and in both cases through gradual enlargement of the caliber of the aforementioned vessels. When the stoppage is in venous vessels, the reinstatement of circulation of the blood will be even more rapid, through adjacent veins, through enlarged capillaries or through anastomosis with choroidal vessels. Moreover, the blood clot can be perforated by one or several channels, and circulation along the occluded vein itself can be resumed. At the same time, small collateral blood vessels are gradually enlarged. At first, they cannot be seen ophthalmoscopically; if they are over the optic disk, they may give the impression of hyperemia, or, if over the retina, they may look like small hemorrhages. Gradually, however, they become visible with the ophthalmoscope and can easily be recognized by their typical appearance of a mesh or of tortuous vessels with many anastomoses, forming a true *rete mirabile*. These new-formed vessels apparently have no purpose, but actually they reestablish the impaired circulation of the blood. The longer any portion of the retina remains deprived of nourishment through lack of circulating blood, the more it deteriorates; and the chances are that the blood vessels adjacent to that part will, in turn, acquire changes which later will cause new hemorrhages. Thus, the sooner the circulation of blood is restored, the better will be the prognosis.

In cases of retinitis proliferans one should discriminate between those in which, after retinal hemorrhages, fibrous tracts from the conjunctiva with few blood vessels are formed at the optical disk and make their way into the vitreous, and other cases in which only a very thin layer of semitransparent conjunctival fibrous tissue sustains a *rete mirabile* of blood vessels. In the first type the condition is a true retinitis proliferans, whereas in the second type the new-formed blood vessels are the expression of an effort to reestablish normal blood flow in a section of the retina where blood circulation was abolished or impaired through the closing of the lumen of arteries or veins.

Retinitis proliferans in cases of the second type, retinal hemorrhages due to various causes, as in the complex generally known as Eales's disease, and retinal changes due to arteritis and both periphlebitis and endophlebitis can all be successfully treated with small doses of roentgen radiation. Vascular dilatation and increased permeability of the endothelium of the capillaries will be accessory to improvement in circulation of the blood, so that insufficient nutrition of the adjacent retina, and ultimately fresh hemorrhages, are avoided and the process of resorption of the existing blood among the nerve cells is hastened. In these cases it would be advisable to use very small doses, of 50 r, at intervals of five days. Miescher's three wave theory indicates that this should be the ideal interval, as the second treatment would coincide with the interval between the first and the second wave, when capillary dilatation would have reached its lowest point.

True retinitis proliferans, of the first type, in which there are fewer new-formed blood vessels and more fibrous tissue tracts, does not respond to small doses of roentgen radiation. It is advisable to use larger doses,



when tumefaction of the nuclei of the endothelium and accumulation of fibroblasts, as in proliferation of the muscular layer, may bring about occlusion of the lumen, with discontinuation of the blood flow, thus breaking up the "vicious circle," which, as the authors have pointed out, may be responsible for fresh hemorrhages. An action on the plasma, increasing its viscosity, might also be considered. The higher sensitivity of the new-formed blood vessels to the roentgen rays explains the excellent results which were obtained.

When small doses of roentgen radiation are given, the anterior portal may be used, as then no damage can be done to the cornea or to the lens, sensitivity of these structures to roentgen rays being much lower than that of the retinal blood vessels. The cornea begins to react only when 800 r is reached, and the crystalline lens only when 500 r is given, whereas 50 r suffices for dilatation of the retinal capillaries. For larger doses, such as those which were used by Dr. Guyton and Dr. Reese, the temporal portal, or the nasal portal when there is no hindrance, should be used.

For roentgen therapy of the retina in its posterior pole, high voltage rays are advisable, as 100 per cent, or even 105 per cent, of the radiation reaches the retina, as a result of the addition of secondary rays, whereas low voltage rays lose their power and only 25 per cent reaches the posterior pole of the globe.

Roentgen treatment for repeated retinal hemorrhages of various kinds and for retinitis proliferans is justified both by the clinical results seen in the last ten years and by knowledge of its *modus operandi*. Moreover, the difficulty in establishing the true etiologic diagnosis in many cases and, as a consequence, the unlikelihood of combating the disease by destroying its primary cause must, perforce, encourage the pathogenic approach to therapy.

The excellent results reported by Dr. Guyton and Dr. Reese with roentgen therapy on 22 eyes with posthemorrhagic new-formed blood vessels in the retina justify my suggestion of the general use of this method, so that a larger number of cases, to be observed over a long period, may enable us to reach definite conclusions.

DR. WILLIAM L. BENEDICT, Rochester, Minn.: Since the application of roentgen therapy to recurrent hemorrhages is not a new procedure, we must consider the variations of the older procedures that have been advocated and used by their authors.

We are somewhat familiar with the remote effects of radiation on ocular structures, even when the eye is not the objective of direct roentgen therapy; therefore, the use of roentgen therapy directed to fundal lesions has been restricted largely because of reticence in initiating pathologic changes that may progress in future years into fibrosis and general degeneration of ocular structures.

I have had no experience with concentrated, directed roentgen therapy, such as has been employed by the authors. I am familiar, however, with the application of roentgen rays in the absorption of extravasated blood in the vitreous and their immediate, and somewhat remote, effect on the proliferation of new retinal vessels.

I have noted the results of this method of treatment of hemorrhagic diseases of the eye in diabetic patients. I have been able to follow the effects over a period of from four to six years of mild doses of roentgen radiation applied directly to the eye, either temporally or through the

pupil. There is no question that blood in the vitreous will be absorbed much more rapidly after irradiation with a dose of 300 to 1,300 r than if the disease is not treated. I am well aware, however, that the retinopathy of diabetes progresses with the age of the patient rather than with the severity of the diabetes, and that the most extensive changes occur in persons whose diabetes begins early in life; regardless of the fact that the diabetes may be well controlled by diet or with the use of insulin, vascular changes progress, first on the venous side and later on the arterial side, and eventually proliferation of new vessels and fibrosis of old thrombosed vessels and hemorrhagic areas occur.

Later studies of the eyes so treated of persons who have had repeated hemorrhages into the vitreous and more or less extensive diabetic retinopathy have shown that the repeated hemorrhages into the vitreous, even of some duration, will disappear more rapidly after the application of comparatively small or mild doses of roentgen rays. However, the proliferative changes in the vessels are not noticeably affected. In no case have I observed diminution in the proliferation of new vessels.

Roentgen irradiation also has been advocated in the treatment of thrombosis or occlusion of the retinal vessels of one cause or another. In most of the patients whom I have treated, unfortunately, such extensive glaucomatous changes have developed that enucleation became necessary, and some other patients have not been followed.

In no case have I seen any definite improvement in the treatment of eyes in which an occlusion of the central vessels with hemorrhage has occurred. I treated a patient with thromboangiitis obliterans more than three years ago. There was no noticeable effect, but the doses used were small and only two applications were given, the total dose being not more than 725 r. I think, therefore, that the new development in this method of treatment consists in the direct application of the rays of high intensity or the use of large doses over very small areas. It is yet to be seen what effect such irradiation will have on the proliferation of vessels in far advanced stages and on the more extensive proliferations that occur not only in diabetic retinitis but sometimes in Eales's disease. There is no question that the immediate effect on the hemorrhagic extravasation to the vitreous will disappear. That, however, is a virtue that cannot be attributed to the high dosage alone.

I should like to know the authors' opinion regarding the value of direct, high-powered irradiation on the proliferation of vessels in cases of advanced diabetic retinopathy with proliferation, the so-called desperate cases, as well as what might be expected ultimately in fibrosis and degeneration of the retinal vessels.

DR. ALGERNON REESE, New York: We have not discussed etiology, first, because it is not within the scope of this paper and, second, because we do not know anything about it. As a matter of fact, we do not know even to what condition the term Eales's disease should be rightly applied. We do know that the term is used to designate a rather heterogeneous group of conditions, as already noted by Dr. Guyton.

Our impression is that Eales's disease proper is a bilateral infectious process having a predilection for both the arteries and the veins of the retina, and frequently affecting also the uvea. The predilection of a causative agent for a certain type of tissue is not unusual. An example is the preference the herpes virus has for nerve tissue.

The purpose of our treatment is not to promote absorption of hemorrhage but to dissipate new-formed blood vessels from which hemorrhage might come. The cases in which the greatest benefit has followed the treatment have been those in which there was the greatest number of new-formed blood vessels of the "rete mirabile" type, with a minimum amount of stroma and organized scar tissue. To date, this regression of the process has been followed by a decrease in the occurrence of retinal and vitreous hemorrhages. As Dr. Guyton emphasized, it is premature to say whether or not the regression and cessation of hemorrhages from this treatment will be permanent.

We are grateful to Dr. Alvaro for pointing out the rationale of the roentgen treatment in these cases. We agree with him that smaller doses of roentgen radiation suffice, and our tendency at present is to reduce the total dose.

Dr. Benedict has rightly emphasized that this treatment consists in directing the rays to the site of the lesion, to the exclusion of the vulnerable anterior part of the eye. This is the most important feature of the treatment and cannot be stressed too much. It is the reason we can give large doses with a minimum of untoward effects.

Dr. Benedict asked about the value of this treatment for diabetic retinopathy. Our experience in this regard is confined to 2 cases, in neither of which was the treatment of benefit. We hope to use the method in a sufficient number of cases to be able to assess the treatment in cases of diabetic retinopathy, in particular those with a large element of new-formed blood vessels.

## STUDIES IN EXPERIMENTAL OCULAR TUBERCULOSIS

### XII. Effect of Streptomycin and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit

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IN PREVIOUS communications<sup>1</sup> there were reported the results of experiments which dealt with the possible therapeutic effect of one antibiotic and two chemotherapeutic agents on experimental ocular tuberculosis. It was found<sup>1a</sup> that penicillin G, given in enormous doses, has no deterrent action on the progress of ocular tuberculosis in the normal (nonimmune) rabbit. It was further reported<sup>1b,c</sup> that two sulfones, "promin" (N,N'-didextrose sulfonate, the sodium salt of p,p'-diaminodiphenyl sulfone) and "promizole" (4,2'-diaminophenyl-5'-thiazolylsulfone) had a deterrent effect on the ocular disease. This was apparent in both the immune-allergic and the normal rabbit, although in the normal animal the effect was not marked. In the normal rabbit, a slight decrease in the ocular inflammation was noted at the end of the second week of treatment, and this was clinically most noticeable after eight weeks of treatment. However, transmission experiments of inoculum from the eyes of the treated animals at the termination of treatment all produced the disease. In the immune-allergic rabbits the effect of treatment was more pronounced. There was a noticeable difference in the clinical picture of the treated and that of the control group at the end of the third week of treatment, and at the conclusion of treat-

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1. (a) Kennedy, J. O.; Woods, A. C.; Buckley, J.; Berthrong, M., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: IX. Failure of Penicillin to Affect the Course of Ocular Tuberculosis, *Arch. Ophth.* **39**:261 (March) 1948; (b) Woods, A. C., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: X. Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, *ibid.* **39**:471 (April) 1948; (c) XI. Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Normal Rabbit, *ibid.* **40**:1 (July) 1948.

ment the histologic evidences of tuberculosis in the eyes of the treated animals were minimal as compared with those in the controls. Moreover, in transmission experiments, the eye of only 1 treated rabbit was found to be infectious. It was concluded that both "promin" and "promizole" had a limited bactericidal effect on *Mycobacterium tuberculosis* and that this therapeutic action became much more evident when a systemic immunity restrained the tuberculous process to limits within the therapeutic range of the drugs.

The observation immediately suggested that "promizole," a nontoxic sulfone which can be administered to human subjects in doses up to 12 or 15 Gm. per day without untoward symptoms, might happily be combined with such an antibiotic as streptomycin in the treatment of ocular tuberculosis. The classic investigations of Feldman and his associates have already conclusively demonstrated the strong deterrent and therapeutic action of streptomycin in experimental tuberculosis in the guinea pig. A recent report by Grignolo<sup>2</sup> on the action of streptomycin alone and of a combination of streptomycin and "promin" on experimental ocular tuberculosis in the normal rabbit indicates that such treatment, begun immediately after inoculation of the eyes, had an inhibitory effect on the later development of lesions during the course of treatment. However, tuberculous disease developed at varying intervals after the cessation of treatment. When treatment was instituted after lesions had appeared in the eyes, no deterrent or therapeutic action was observed.

There are numerous reports of favorable clinical action in various forms of human tuberculosis, but only fragmentary mention of its effect in clinical ocular tuberculosis. The early scarcity of streptomycin, the untoward side effect sometimes observed—vestibular damage, the development of sensitivity and the development of resistance to the drug by the *Myco. tuberculosis*, with the possibility that systemic lesions will be lighted up—all appear to have restrained ophthalmologists from using it in the treatment of clinical ocular tuberculosis. As a result, the occasional scattered mention of the use of streptomycin in cases of clinical ocular tuberculosis does not provide sufficient data to permit any conclusions as to the merits and danger of such therapy. It is evident that this field should be explored. It is also evident that, in view of the danger of recurrence after the maximum of streptomycin therapy has been given, happier therapeutic results might be obtained if some effective chemotherapeutic agent could be administered in conjunction with streptomycin and continued after streptomycin therapy has been terminated. A case in point was recently observed in the Wilmer

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2. Grignolo, A.: *Primi risultati sperimentali e clinici sull'impiego della streptomicina nelle infezioni tubercolari dell'occhio*, *Minerva med.* 1:16, 1948.

Institute, that of a young Negro girl who had been energetically treated with streptomycin alone for tuberculous meningitis, from which she had made a complete symptomatic recovery. Three months after injections of streptomycin has been stopped, widespread, acute, caseating ocular tuberculosis developed in one eye, resulting in its loss.

The idea of combining an effective sulfone with streptomycin is not new. As early as 1945, Smith and McClosky<sup>3</sup> reported on the combination of streptomycin and "promin" in the treatment of experimental tuberculosis in mice and rats. They found the chemotherapeutic index of streptomycin ten times that of "promin," but the combination of streptomycin and "promin" gave three times the effect that might be expected from mere summation, indicating a synergistic action. In a later report,<sup>4</sup> in which their data were obtained from direct tissue smears, subculture of lung suspensions and subinoculation of lung suspensions in guinea pigs, they found little, or no, deterrent effect with "promin" alone and a moderate depressant action with streptomycin, but sterilization in 41.6 per cent of their animals after treatment with the two drugs. A recent clinical report by Lincoln and her associates<sup>5</sup> indicates favorable results in the treatment of miliary tuberculosis in children with "promizole" alone.

#### EXPERIMENTAL STUDY<sup>6</sup>

*Determination of Dosage.*—The first question to be determined was that of dosage. This had already been worked out for "promizole" by Feldman, and in the previous studies of this series it was found that 1 per cent "promizole" added to the diet provided an approximate daily dose of 1.25 Gm. of the substance and produced a blood level that ranged as high as 1.9 mg. per hundred cubic centimeters. This was the dose of "promizole" administered in this experiment.

In Feldman's original experimental work with streptomycin, the drug was given at six hour intervals. The usual practice is to administer streptomycin every three or six hours to clinical patients. Molitor,<sup>7</sup> for example, stressed the need of giving streptomycin every three hours in order to maintain an effective concentration. Recent investigations have clearly indicated, however, that such frequent administration is unnecessary to obtain the full therapeutic effect. Thus Feld-

3. Smith, M. I., and McClosky, W. T.: The Chemotherapeutic Effect of Streptomycin and Promin in Experimental Tuberculosis, Pub. Health Rep. **60**: 1129, 1945.

4. Smith, M. I.; McClosky, W. T., and Emmart, E. W.: Influence of Streptomycin and Promin in Proliferation of Tubercle Bacilli in the Tissue of the Albino Rat, Proc. Soc. Exper. Biol. & Med. **62**:157, 1946.

5. Lincoln, E. M.; Stone, S., and Hoffman, O. R.: The Treatment of Miliary Tuberculosis with Promizole, Bull. Johns Hopkins Hosp. **82**:56, 1948.

6. The streptomycin sulfate used in this experiment was given by Chas. Pfizer & Company, Inc., and the "promizole," by Parke, Davis & Company.

7. Molitor, H.: Pharmacology of Streptomycin, Bull. New York Acad. Med. **23**:196, 1947.

man<sup>8</sup> found in guinea pigs treated once, twice and four times daily, or four times daily on alternate weeks (all animals receiving the same amounts of streptomycin), that the numerical index of infection after a minimum of three weeks' treatment varied from 3.2 to 6.0 with the different doses, as compared with an index of 85.3 for the untreated controls. In other words, there was no practical difference in the therapeutic results when streptomycin was administered less often. Corper and Cohn<sup>9</sup> showed that the same effect in prolonging the lives of animals with an otherwise lethal infection was obtained when streptomycin was given every five days. The report by the Veterans Administration to the Council on Pharmacy and Chemistry of the American Medical Association<sup>10</sup> indicated that involvement of the vestibular branch of the eighth nerve occurred in 96 per cent of patients receiving 2.0 Gm. of streptomycin daily in divided doses. At the fourth Streptomycin Conference of the same groups, it was reported<sup>11</sup> that, in man, equally favorable therapeutic effects were obtained with, and the patients did quite as well on, 0.5 Gm. of streptomycin every twelve hours as they did on the same dose given more frequently, i. e., 0.5 Gm. every six hours. Further, the toxic reactions were much less, involvement of the vestibular branch of the eighth nerve occurring in only 17 per cent of the patients receiving 0.5 Gm. every twelve hours. The occurrence of other toxic reactions was less reduced, and no difference was found in the development of resistance by the isolated tubercle bacilli.

In the light of these investigations, the streptomycin in these experimental animals was administered once a day only. The dose was 50 mg. per kilogram of body weight. This dose was well tolerated. During the course of the experiment only 1 of the treated animals died, and this of an incidental cage infection, unrelated to tuberculosis or treatment. This mortality rate was well below that expected in the light of our previous experiments with tuberculous rabbits. This dose of "promizole" and streptomycin produced blood levels up to 7.6 mg. per hundred cubic centimeters for streptomycin, the blood being taken one and one-half hours after the administration of the streptomycin. The high level for "promizole" was 5.1 mg. per hundred cubic centimeters, and the mean of the various determinations was 1.7 mg. per hundred cubic centimeters.<sup>12</sup>

*Plan of the Experiment.*—On June 19, 1947, 66 rabbits were inoculated in the groin with 0.5 cc. of a six week old culture of a virulent human strain of Myco. tuberculosis. The rabbits were entirely asymptomatic, and on Jan. 22, 1948,

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8. Feldman, W. H.; Henshaw, C. H., and Karken, H. G.: Frequency of Administration of Streptomycin: Its Influence in Results of Treatment in Guinea Pigs, *Am. Rev. Tuberc.* **55**:435, 1947.

9. Corper, H. J., and Cohn, M. L.: The Remote Sustained Threshold Therapeutic Action of Streptomycin in Tuberculosis, *Science* **106**:446, 1947.

10. The Effects of Streptomycin on Tuberculosis in Man, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **135**:634 (Nov. 8) 1947.

11. Dosage of Streptomycin in Tuberculosis, *Current Comment*, **135**:842 (Nov. 29) 1947.

12. The blood levels for both streptomycin and "promizole" were determined by Dr. E. Kennerly Marshall, Professor of Pharmacology of the Johns Hopkins University School of Medicine. The technic of determinations has been reported by Dr. Marshall and his associates (Marshall, E. K., Jr.; Blanchard, K. C., and Buhle, Emmett L.: Colorimetric Methods for Determination of Streptomycin, *J. Pharmacol. & Exper. Therap.* **90**:367, 1947).

there were 64 survivors, all in excellent condition. Intracutaneous tests with purified protein derivative U. S. P. showed that all rabbits had a moderate degree (1 plus reaction) of cutaneous hypersensitivity. On January 22, all the rabbits were given an injection into the anterior chamber of 0.2 cc. of the paper filtrate of a six week old culture of the same organisms so adjusted that each oil immersion field contained approximately 200 bacilli. At the time of the ocular inoculation, the sensitivity of this organism to streptomycin was determined, and it was found that the tubercle bacillus used was sensitive to 1 microgram per cubic centimeter of streptomycin.

All rabbits showed the usual immediate reaction to the tuberculin in the inoculum, manifested by ciliary congestion and the usual evidences of nongranulomatous iritis, the symptoms coming on twenty-four hours after the inoculation and lasting about three days. Thereafter, the eyes were practically asymptomatic for about ten days, when low grade ciliary congestion, slight haziness of the cornea and evidences of inflammation in the iris developed. By February 11, three weeks after inoculation, these symptoms were definite, and miliary tubercles appeared on the iris or in the cornea or in both. The degree of tuberculous activity in each rabbit was then evaluated on a numerical scale (0 to 4), just as was done in the former experiments in this series. The rabbits were then divided into three groups of 21 each, each group having tuberculous activity of the same average severity. In actual figures, group 1, the control group, had an average reaction of 0.8; group 2, which received streptomycin alone, an average reaction of 1.0, and group 3, which received both streptomycin and "promizole," an average reaction of 1.1. Thus, the figures were weighted slightly against the treated animals in that they represented severer initial reactions than did those for the control series. Treatment was started on February 11, with the dose already outlined, group 1 receiving no treatment; group 2 received 50 mg. of streptomycin alone in one daily injection; group 3 received the same amount of streptomycin per kilogram of body weight plus 1 per cent "promizole" added to their food. Thereafter, each animal was examined carefully clinically once a week; the degree and intensity of ocular tuberculosis were estimated, and the average activity for each group was thus determined and recorded.

On April 27, when treatment was terminated, 6 animals from group 1 (fair specimens of the control group, with an average activity of 1, this being the average for the entire group), 6 animals of group 2 and 6 animals of group 3 were killed and autopsied and their eyes removed for histologic section. Six other rabbits, of groups 1, 2 and 3, were similarly killed and the injected eyes removed. These eyes were opened under aseptic precautions, and the uveal tracts dissected out and ground up in a test tube with sterile sand in 1.5 cc. of sterile saline solution. The supernatant fluid was decanted and cultured; 0.2 cc. of this extract of the uveal tract was injected in the anterior chamber of the eye of a normal rabbit to determine whether the uveal tracts of the control and the treated animals were infectious. The remaining rabbits, 8 in group 1 (controls), 7 in group 2 and 8 in group 3, were kept for further observation to determine whether there were any recurrences after cessation of treatment.

## RESULTS

*Clinical Course.*—The composite results of the clinical courses of the three groups are shown in figure 1, in which the ordinate represents the degree of the average intensity of the ocular tuberculosis and the



abscissa represents the time, in weeks. Thus, at the end of one week of treatment there was a slight, but statistically insignificant, change in favor of the two treated groups. At the end of the two weeks, this change was pronounced, and at the end of the fourth week it was most striking. At this time the disease in the control group had advanced and the average activity of the group was 2, while the average for the two treated groups had dropped to 0.26 and 0.25, respectively. While the figures for group 2 and group 3 were identical at this time, the general improvement was much more striking in group 3, treated with the combination of streptomycin and "promizole." Thus, in group 2, there were 6 animals with activity rated as 0 (completely inactive clinically) and 6 rated as showing a trace of activity, while 7 had activity. In group 3, 11 animals were rated as showing no activity, and 6, as showing only a trace, while only 3 had activity. One appar-

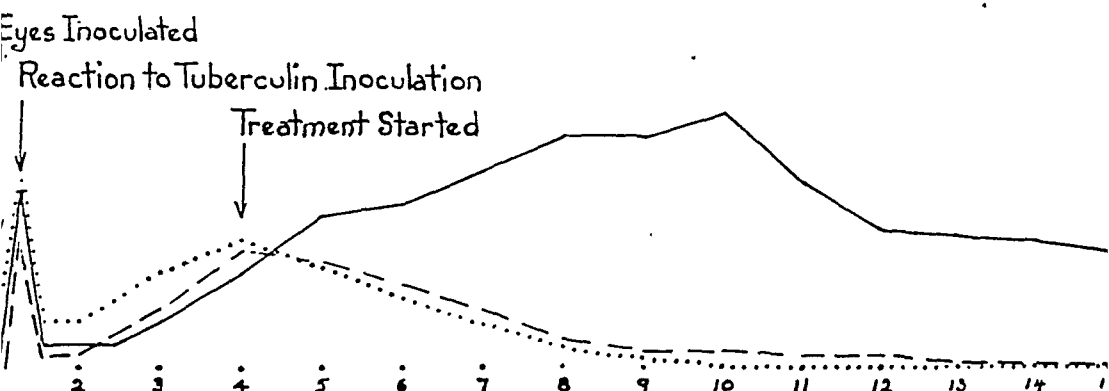


Fig. 1.—Graph illustrating clinical course in rabbits of groups 1, 2 and 3. The values for the untreated group (group 1) are shown by the solid line; those for the group treated with streptomycin alone (group 2), by the line of dashes, and those for the group treated with streptomycin and "promizole," by the line of dots.

The intervals indicated on the line of ordinates represent 0.1 on the numerical scale used for grading tuberculous activity.

ently nonimmune rabbit with severe and resistant ocular tuberculosis accounted for the greater part of the activity in group 3 at this time.

On March 23, after six weeks of treatment, the untreated (control) group was at its height of activity, the average being 2.2. At the same time, in group 2, there were 12 rabbits with a rating of 0 and 6 with only a trace of activity, while only 3 were rated as showing activity. In group 3, 14 rabbits were given a rating of 0 clinically, and the remaining 6 showed only a trace of activity, none being rated as having active tuberculosis. On April 6, after eight weeks of treatment, all rabbits in the control group had activity, although the tuberculous inflammation was definitely declining, the average rating being 1.3. In group 2, 15 rabbits had a rating of 0, and the remaining 4 showed only a trace of activity. In group 3, all 20 rabbits had a rating of 0, showing only

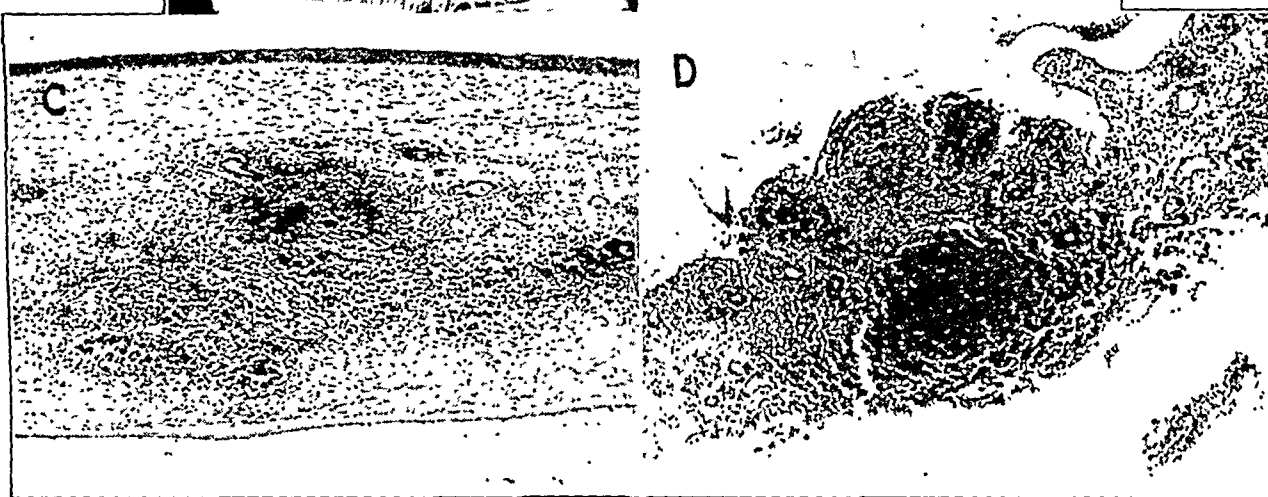
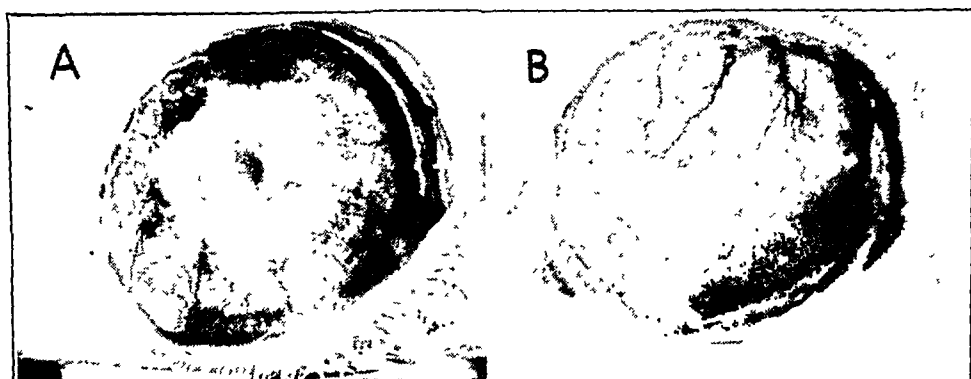


Fig. 2 (rabbit 7, group 1).—*A*, cornea on February 25; *B*, cornea on April 28; *C*, cornea showing scattered hard tubercles; *D*, iris with a large, hard tubercle.

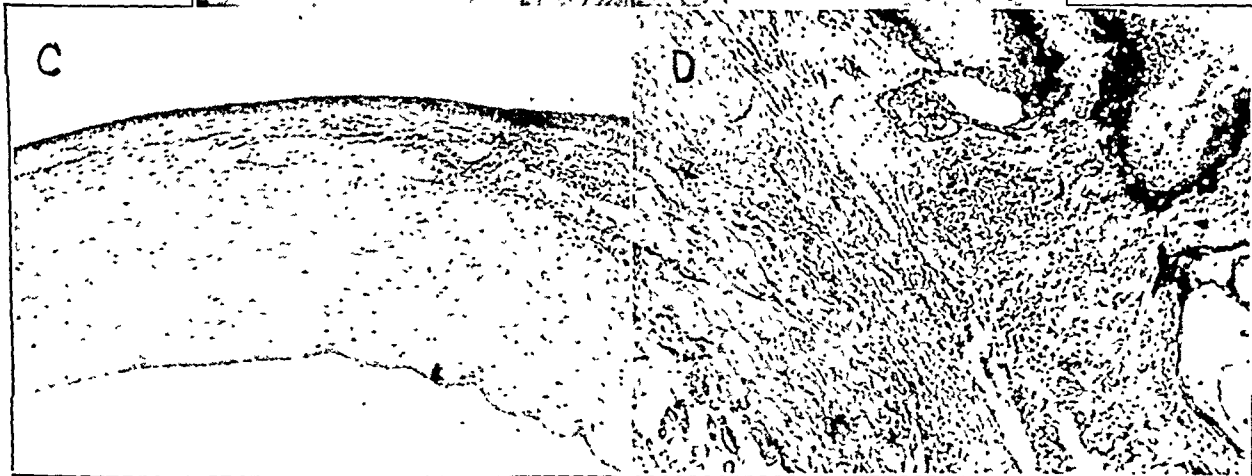
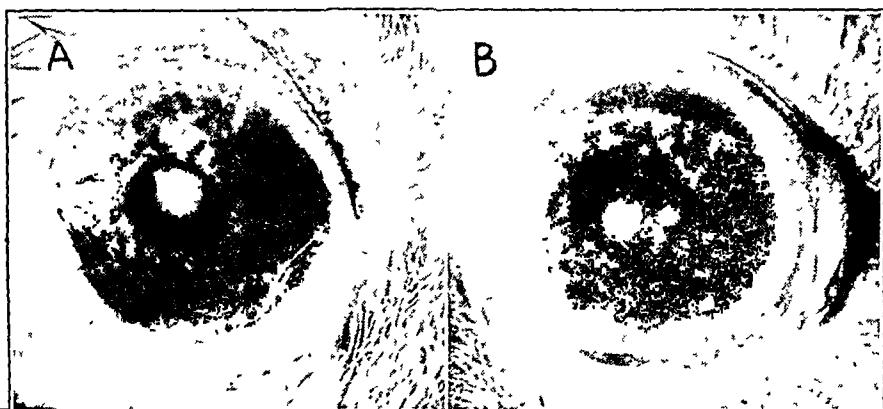


Fig. 3 (rabbit 14, group 1).—*A*, eye on February 25; *B*, eye on April 28; *C*,

the scars of the former inflammation and no traces of activity whatsoever. On April 27, seventeen weeks after the inoculation, the control group was beginning to show the usual spontaneous healing observed in immune-allergic rabbits, 3 animals being recorded as showing no activity and 2 others as showing only a trace, while the remaining 15 were recorded as having definite activity, the average for the group being 1. In groups 2 and 3, the activity of all rabbits was rated as 0, there being

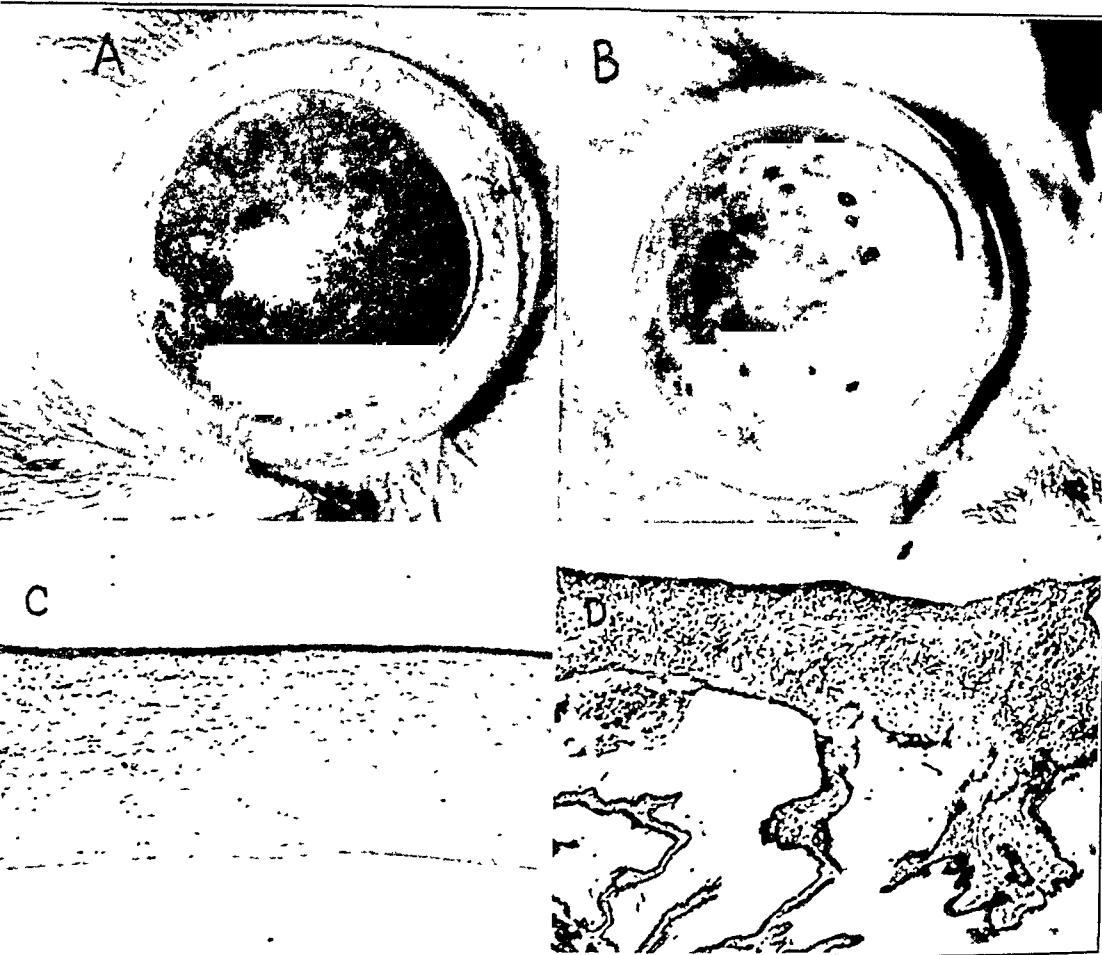


Fig. 4 (rabbit 13; group 2).—*A*, eye on February 25, at beginning of streptomycin therapy; *B*, eye on April 28, after completion of streptomycin therapy; *C*, cornea and limbus, showing minimal infiltration of cornea; *D*, iris, showing small active tubercle on posterior surface and healed tubercle of stroma.

no trace of any active inflammation in any of the treated animals. Treatment was stopped on this date. *A* and *B* of figure 2 are photographs of the eye of an untreated (control) rabbit (group 1, rabbit 7) taken on February 11 and April 27, respectively. This rabbit was the most severely affected of the untreated group. *A* and *B* of figure 3 show the eye of another untreated control, the least severely affected of the rabbits of

group 1, taken on the same dates. These photographs therefore illustrate the high and low extremes of untreated ocular tuberculosis in immune-allergic rabbits.

The clinical appearance of 2 rabbits of group 2, before and after treatment, are shown in figures 4 *A* and *B* (rabbit 13) and 5 *A* and *B* (rabbit 17), which illustrate the fading of ciliary congestion, the clearing of the cornea and the absorption of the tubercles in the iris.

The course of the disease in the rabbits of group 3 is shown in figures 6 *A* and *B* (rabbit 35) and 7 *A* and *B* (rabbit 37). These

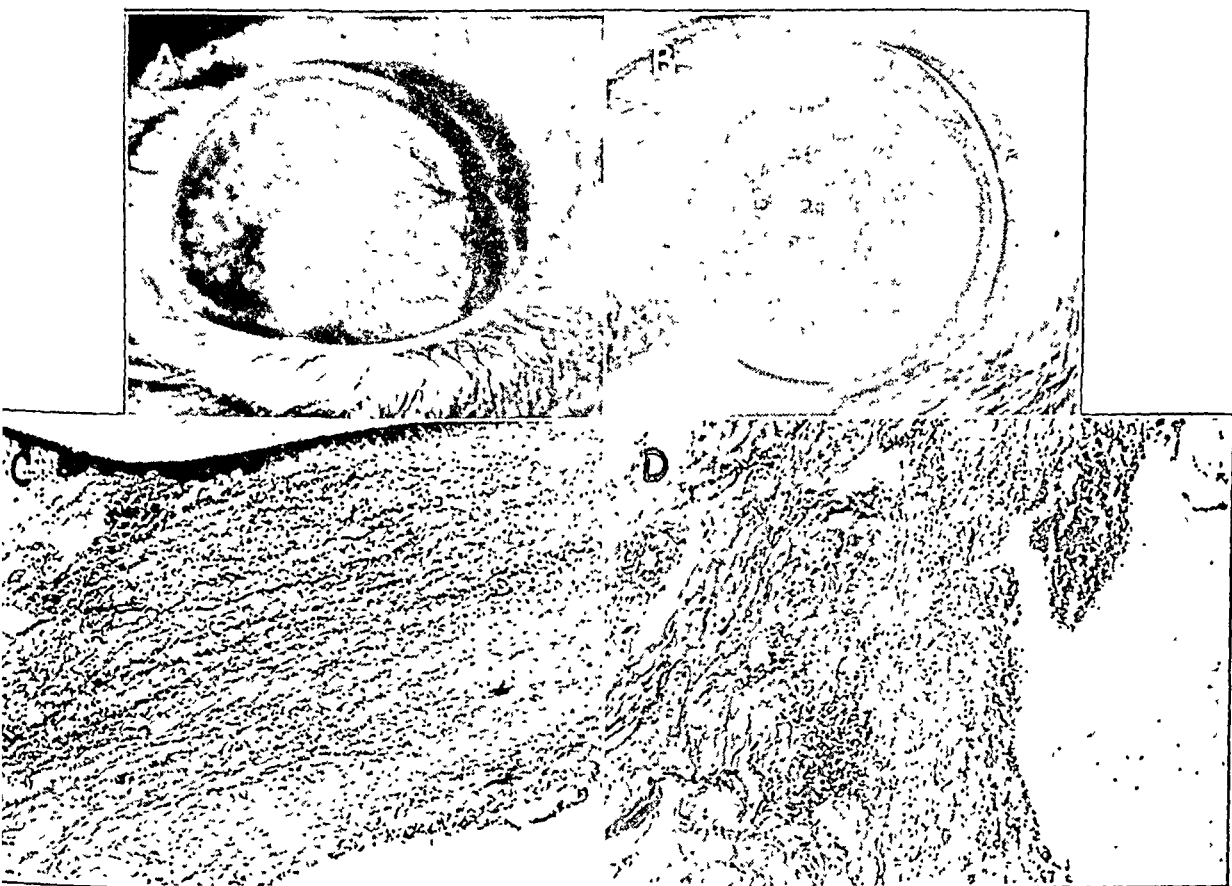


Fig. 5 (rabbit 17; group 2).—*A*, eye on February 25, at beginning of streptomycin therapy; *B*, eye on April 28, after completion of streptomycin therapy; *C*, minimal infiltration of limbus and root of iris; *D*, root of iris and ciliary body, showing small tubercle and moderately intense cellular infiltration.

figures illustrate the more dramatic clinical results shown by the animals treated with the combination of streptomycin and "promizole." Thus, figures 6 *A* and 7 *A* show the appearance of the eyes on February 11, when treatment was started, with ciliary congestion, moderate uveal inflammation, contracted pupil and many tubercles scattered over the surface of the iris, and figures 6 *B* and 7 *B* illustrate the appearance on April 27, with complete absorption of the tubercles of the cornea and iris.

*Histologic Features.*—Histologic examination of the eyes of the rabbits killed for study showed a distinct difference in the pictures of the three groups.

GROUP 1 (untreated controls): The picture was that usually seen in the secondarily inoculated eyes of immune-allergic rabbits. There were numerous hard tubercles throughout the cornea, iris and ciliary body, with moderate to severe mononuclear and epithelioid cell infiltration of the angle, iris and ciliary region. Only occasionally were any areas of caseation and necrosis noted. There were practically no lesions anywhere in the posterior ocular segment.

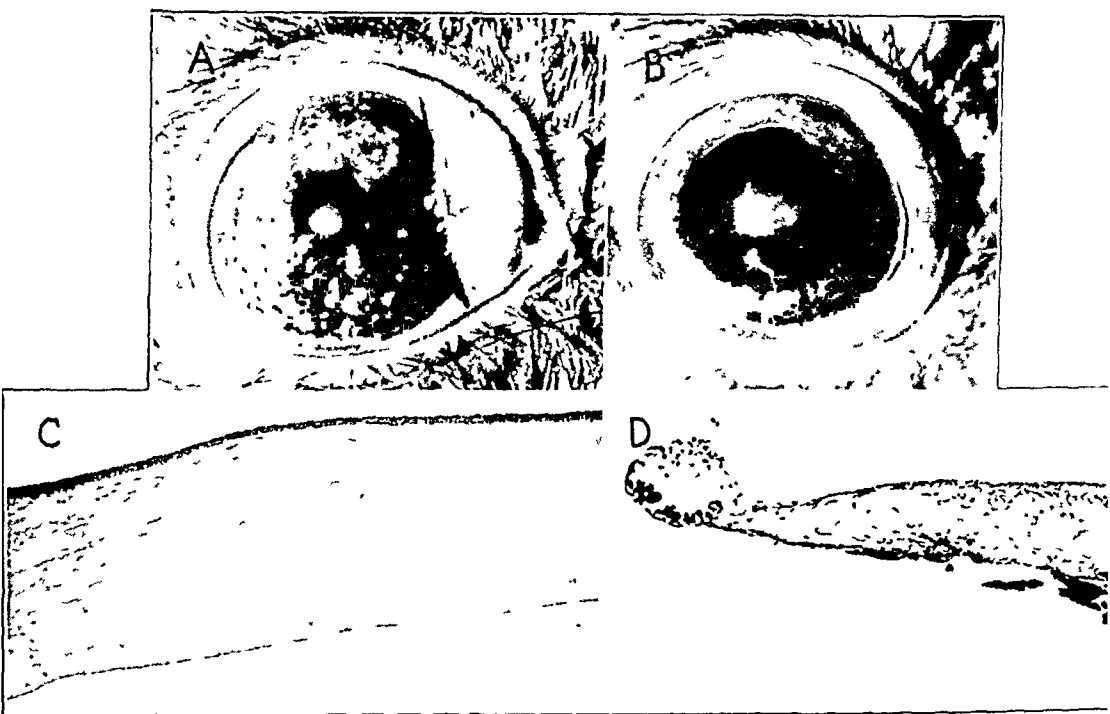


Fig. 6 (rabbit 35, group 3.—*A*, eye on February 25, before beginning of streptomycin and "promizole" therapy; *B*, eye on April 28, after completion of therapy; *C*, cornea, showing minimal scarring; *D*, healed tubercle on tip of iris.

The appearance of the eyes of the rabbits of group 1 is illustrated in figures 2 *C* and *D* and 3 *C* and *D*. In the most severely involved of the controls (rabbit 7; figs. 2 *C* and *D*) there were dense cellular infiltration, with many large, hard tubercles and one area of caseation and necrosis (not shown in figure). *C* and *D* of figure 3 show, respectively, the cornea near the limbus and the iris and ciliary body of the least severely involved of the animals of group 1 (rabbit 14). There was moderately severe infiltration of the cornea near the limbus; elsewhere the cornea was clear. The iris and ciliary body were more severely involved, showing hard tubercles and some diffuse cellular infiltration.

GROUP 2 (treatment with streptomycin alone): The picture was much less severe than that in the untreated controls. Careful study of the sections, however, revealed in all eyes minimal to moderate evidences of active tuberculosis. Such evidences consisted in occasional

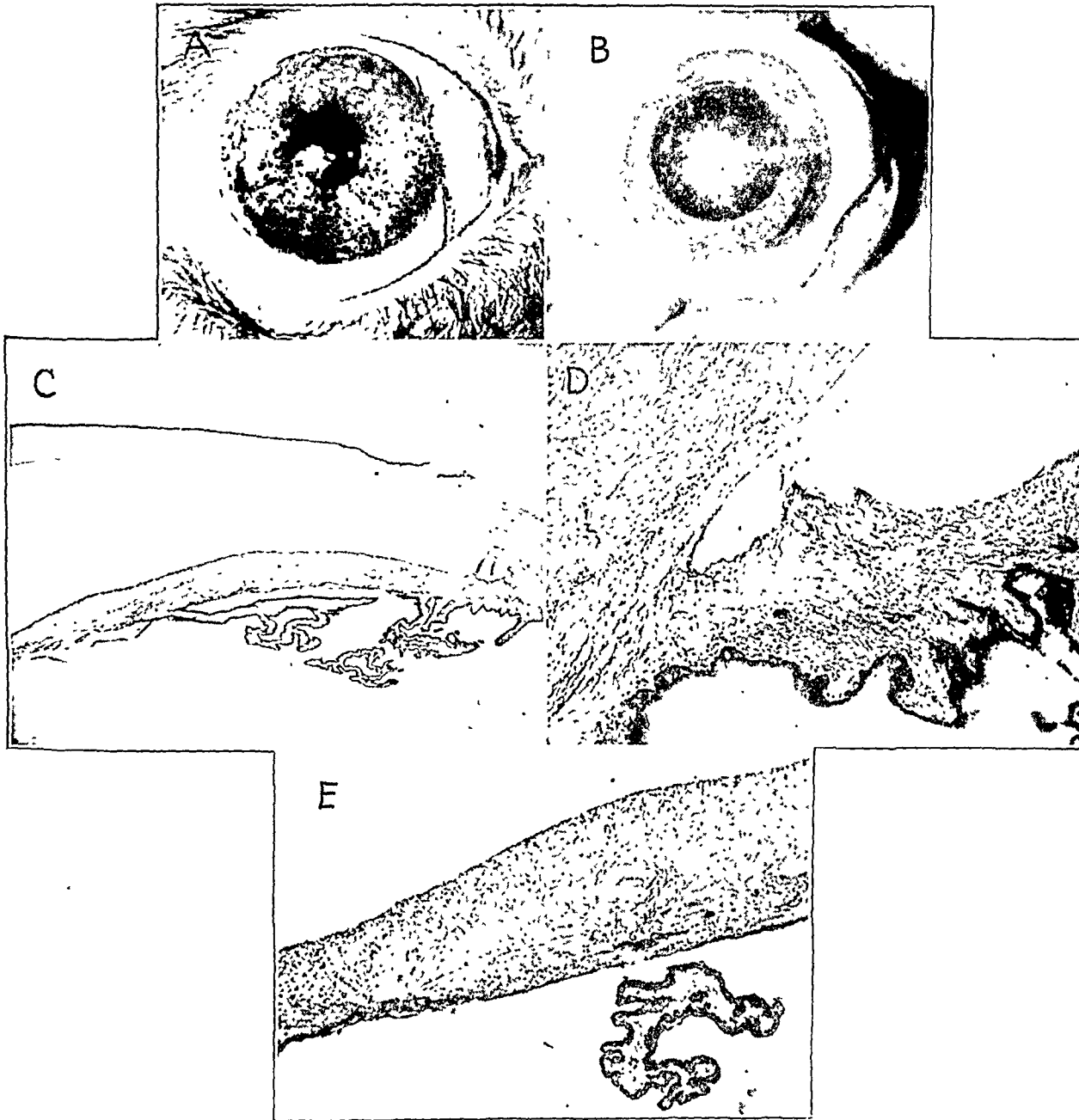


Fig. 7 (rabbit 37, group 3).—*A*, eye on February 25, before beginning of streptomycin and "promizole" therapy; *B*, eye on April 28, after completion of therapy; *C*, anterior segment, showing normal cornea; *D*, root of iris, showing possible minimal infiltration with scarring, and *E*, iris with few persisting wandering cells.

areas of mononuclear and epithelioid cell infiltration and in occasional small tubercles, usually on the posterior surface of the iris rather than in the stroma, giving the impression that the tubercle bacilli faded rather

better in the ocular fluids than in the stroma. There was abundant scarring, and in many places healed tubercles occurred. However, every eye examined in this group still showed histologic evidence of at least minimal activity.

Typical lesions of the rabbits of group 2 are shown in figures 4 *C* and *D* and 5 *C* and *D*. These sections show slight, but definite, evidences of smoldering activity, despite the negative clinical appearance. Figure 4 *C* shows minimal infiltration of the cornea; figure 4 *D*, a very small tubercle, or Koeppe nodule, on the posterior surface of the iris, free in the posterior chamber. Figure 5 *C* shows minimal infiltration in the cornea near the limbus in rabbit 17, while figure 5 *D* shows a small tubercle near the root of the iris and moderate cellular infiltration in the ciliary area.

GROUP 3 (treatment with a combination of streptomycin and "promizole"): Histologic evidences of tuberculosis was much less than in the rabbits of group 2, which were treated with streptomycin alone. The only evidence of activity found in any of these eyes consisted in minimal infiltration with wandering cells in the iris and corneal stroma. The persistence of wandering cells in the stroma of the cornea, iris and ciliary body can scarcely be considered evidence of an active tuberculosis in eyes which two months previously had been the site of active disease. It is probable that they are only the residua of the infection. There were many healed and encapsulated tubercles and no active ones. In the main, the tissue of the anterior ocular segment appeared essentially normal, and there were no lesions in the posterior segment.

Figure 6 *C* shows the cornea of rabbit 35, with minimal scarring still visible. Figure *D* shows a healed tubercle at the tip of the iris in the same rabbit.

Figure 7 *A* shows a low power view of the anterior segment of rabbit 37, with an essentially normal-appearing cornea and iris; *B*, the root of the iris in the same rabbit, with definite scarring in the iris and a few wandering cells throughout the stroma, and *C*, another section of the same iris with a few wandering cells. The persistence of wandering cells in the stroma of the cornea, iris and ciliary body can scarcely be considered evidence of active tuberculosis in eyes which two months previously had been the site of active disease. It is probable that they are only the residua of the infection. No definitely active lesions could be seen in the eyes of the rabbits of group 3.

*Transmission Experiments.*—On April 27 and 28, 6 animals from each group were killed for transmission experiments. The diseased eyes were removed and the uveal tracts dissected out, and a saline extract of the tissue was prepared, as previously described, and inoculated into the anterior chambers of the eyes of normal rabbits. The results of these experiments were as follows:

GROUP 1: In the eyes of all the normal rabbits inoculated with extracts of the uveal tissue of the untreated controls a frank, outspoken ocular tuberculosis had developed by May 18. The incubation period ranged from fourteen to twenty-one days. The ocular tuberculosis ran the usual course of the disease in normal rabbits, and the tuberculous nature of the inflammation was confirmed by histologic examination of the eyes.

GROUP 2: In 3 of the transfer rabbits frank, typical ocular tuberculosis developed in the inoculated eyes. The incubation times were, respectively, sixteen, thirty-one and thirty-one days, with an average of twenty-six days. After development of activity, the disease ran the usual course of ocular tuberculosis in the normal rabbit. The inoculated eyes of the other 3 rabbits remained normal during the period of observation (up to June 19). Thus, the extracts of the uveal tissue from 50 per cent of these rabbits were noninfectious on subinoculation.

GROUP 3: In 3 of the transfer rabbits ocular tuberculosis developed in the inoculated eyes. The incubation periods were twenty-four, thirty-eight and thirty-eight days, respectively, with an average of thirty-three days. The eyes of the other 3 transfer rabbits remained normal during the entire period of observation (eight weeks), the transfer material being noninfectious.

The finding that 50 per cent of the treated animals in groups 2 and 3 had infectious uveal tracts is in contrast with the result in a previously reported experiment in which immune-allergic rabbits with ocular tuberculosis were treated with "promin" or "promizole" alone. In this experiment only 1 of 7 of the transferred uveal extracts was infectious. This discrepancy is probably accounted for by the different technic used in the preparation of the uveal extract. In the transfers from rabbits treated with "promin" or "promizole," the uveal tracts were macerated in a mortar with sand and 5 cc. of saline solution. The greater amount of diluent used in these previous transfers probably accounts for the lower incidence of positive results.

*Cultures.*—After the extracts of uveal tissue from the three groups had been prepared, each extract was cultured on Petraghini medium immediately before the ocular inoculations were made in the transfer rabbits. The results of these cultures were as follows:

GROUP 1: All cultures from the untreated controls were positive. Colonies were noted as early as the second week, and many colonies were macroscopically visible at the end of four weeks. At the end of eight weeks the slants of these 6 cultures showed the following number of colonies: 15, 30, innumerable, 11, 28 and 16. Microscopic examination of these colonies, stained for acid-fast organisms, showed pure cultures of tubercle bacilli.



GROUP 2: Three of the 6 cultures were positive for tubercle bacilli and 3 were negative. The growth, however, was exceedingly scanty. On 2 of the positive cultures there was only one colony, and on the third, only two colonies. These colonies were first detected on June 1, five weeks after inoculation. The transfer rabbits inoculated with 2 of the positive cultures showed ocular tuberculosis, while the third transfer rabbit, inoculated with an extract which showed only one colony, did not have the disease. Smears from these 3 positive tubes showed pure cultures of tubercle bacilli. Smears from the negative tubes showed no organisms.

GROUP 3: There was no macroscopic growth of any kind on any of the 6 cultures. Smears were made from all tubes and stained for tubercle bacilli by the usual technic for acid-fast organisms. Five of these smears were negative for the organisms. The sixth smear showed an occasional tubercle bacillus, despite the fact that there were no macroscopic colonies.

The bacilli recovered from the rabbits of group 2 were then tested for their sensitivity to streptomycin, to determine whether any resistance had been developed by the organism through treatment with streptomycin. The results of these studies of sensitivity will be reported later.

*Recurrences.*—After the completion of treatment, on April 26, 9 rabbits from group 1, 8 rabbits from group 2 and 9 rabbits from group 3 remained after their companions had been killed for histologic study and transmission experiments. These animals were kept under observation for a further period of eight weeks without treatment, to observe whether any relapses occurred in the eyes of the treated rabbits after cessation of treatment.

The disease in the rabbits of group 1 ran the usual course, with gradually waning activity, so that, on June 19, 7 of the 9 had no clinical activity, while the remaining 2 showed an average activity of 1.0.

Of the rabbits of group 2, which were treated with streptomycin alone, 3 had relapses. In 1 of these (rabbit 16) the relapse occurred on May 4, one week after cessation of treatment, and in the other 2 (rabbits 52 and 53), on May 11, two weeks after cessation of treatment, the average period of remission being twelve days. All these eyes with a relapse of the disease continued to show moderate activity during the period of observation, up to June 19. On this date the degrees of activity were, respectively, 0.5, 1 and 2. Three rabbits in this group died within one month after cessation of treatment. Unfortunately, these animals died over a weekend, and the bodies were discarded without a general autopsy, the eyes alone being removed for section. Up to the time of death, there had been no ocular exacerbations in these rabbits. Histologic examination of the enucleated eyes

showed only the same minimum to moderate degree of tuberculous activity noted in the eyes of the other rabbits treated with streptomycin alone.

None of the rabbits of group 3 had relapses until June 1, thirty-four days after cessation of treatment. On this date, 1 rabbit showed a slight trace of recurring inflammation, which persisted, without progression, during the remaining three weeks of observation.

A summary of the observations on transmission experiments, cultures and recurrences are shown in the accompanying table.

#### COMMENT

These results speak for themselves. Streptomycin alone has a strongly deterrent action on ocular tuberculosis in the "immune-allergic"

*Summary of Observations on Transmission Experiments, Cultures and Recurrences in Rabbits with Ocular Tuberculosis Treated with Streptomycin and/or "Promizole"*

	Transfer Experiments		Cultures of Uveal Extracts		Recurrences	
	Results	Incubation Period, Days	Results	Incubation Period	Results	Period of Remission, Days
Group 1 (untreated controls)	100% positive	17	100% positive for tubercle bacilli	Heavy growth in 4 weeks	Gradually waning activity	
Group 2 (streptomycin alone)	50% (3) positive; 50% (3) noninfectious	26	50% (3) positive for tubercle bacilli; 50% (3) negative	1-2 colonies in 5 weeks	3 out of 8 (37%)	12 (average)
Group 3 (streptomycin and "promizole")	50% (3) positive; 50% (3) noninfectious	33	83% (5) negative; 17% (1) positive	Microscopic growth in one culture only in 8 weeks	1 out of 9 (11%) (minimum reaction)	34

rabbit, but clearly, under the conditions of this experiment, in the doses given over the period of treatment, did not exert a completely bactericidal action on the tubercle bacilli in the sense that the bacilli were uniformly destroyed in all animals. Despite the appearance of complete clinical inactivity, there remained minimal to moderate microscopic evidences of tuberculous activity in all the eyes examined histologically. After cessation of treatment, the disease in the eyes of 3 rabbits treated with streptomycin alone relapsed rather promptly and continued to smolder over a six or seven week period of observation. The extracts of uveal tissue from 3 eyes of the rabbits treated with streptomycin alone were infectious, while those from the other 3 were noninfectious. Three of the cultures of these uveal extracts were positive for tubercle bacilli. Thus, while streptomycin alone produced pronounced clinical improvement, it could not be called a "cure" for ocular tuberculosis.

Histologic examination of the eyes of the rabbits treated with streptomycin alone indicated a strong bacteriostatic, but certainly very incomplete, bactericidal action on the tubercle bacilli. That such a bacteriostatic action and incomplete bactericidal action exist was confirmed by the fact that after cessation of treatment there were recurrences in 3 of the 8 surviving rabbits of this group. That there was some bactericidal action, however, is indicated by the fact that in 3 of the transfer rabbits the disease did not develop, the inoculated uveal extracts being noninfectious, and also by the fact that the cultures of these extracts were negative for the bacilli in 3 instances, while the 3 positive cultures showed only one or two colonies. This is in contrast with the results for the control group, in which transfer material gave positive results in 100 per cent of the experiments and the uveal tissue extracts yielded from 11 to innumerable colonies on culture.

When streptomycin and "promizole" were used together, the effect on the clinical course of the disease was greater than when either agent was used separately. The difference in the histologic picture was most striking, there being practically no microscopic evidence of any active tuberculosis in any of the rabbits treated with the combination of the two agents. From the histologic picture alone, one could well conceive of a complete bactericidal action on the tubercle bacilli. Such a complete action, however, was not confirmed by the transmission experiments, by the cultures of the uveal tissue extract or by recurrences in the survivors. In the transmission experiments, the results were somewhat similar to those in which the transfer material was from rabbits treated with streptomycin alone—there were 3 positive transfers in 6 experiments. The incubation period was, however, somewhat longer, thirty-three as against twenty-six days. There was a difference also in the results of culture of the uveal tissue extracts, the cultures of the tissue extracts of the rabbits treated with streptomycin and "promizole" yielding no tubercle bacilli in 5 instances, while the sixth culture showed only a microscopic growth. The results indicate that few viable bacilli must have remained in the uveal tracts of these rabbits. Further, there was only 1 recurrence in the 9 survivors of group 3. It seems fair, therefore, to postulate that, under the conditions of this experiment, the combination of streptomycin and "promizole" exerted a strong bactericidal action against the tubercle bacilli, in addition to the bacteriostatic action. From this accumulated evidence, it is a logical deduction that had the streptomycin-"promizole" treatment been continued longer, a complete bactericidal action might have been attained.

Since "promizole" is nontoxic, and can apparently be given indefinitely to both animals and man, these experiments suggest further that if the clinical disease can be controlled by combined treatment with

streptomycin and "promizole," the more toxic streptomycin might be discontinued and the administration of "promizole" continued until either complete bactericidal action or encapsulation of the lesions has taken place.

#### SUMMARY AND CONCLUSIONS

Streptomycin exerted a deterrent action on the course of ocular tuberculosis produced by inoculation of the eyes of immune-allergic rabbits. The improvement in the clinical picture was noted after nine days of treatment and was definite in sixteen days. After four weeks of treatment, the disease was clinically inactive in 15 of 20 rabbits, and after eight weeks of treatment it was clinically inactive in all.

Despite the absence of clinical evidences of activity, histologic examination of the eyes of these rabbits showed minimal to moderate degrees of tuberculous activity. In transmission experiments, 3 of 6 rabbits showed infectious uveal tracts in the diseased eyes, and cultures of extracts of these tissues yielded tubercle bacilli in 3 instances. After cessation of treatment, active exacerbation of the tuberculosis occurred in 3 of 8 rabbits under continued observation.

The combination of streptomycin and "promizole" in the treatment of similar ocular tuberculosis in immune-allergic rabbits produced a more dramatic therapeutic response than was obtained with streptomycin alone. After four weeks of treatment, the disease in all 21 rabbits so treated appeared clinically inactive and so remained throughout the period of treatment. Histologic examination of the eyes of these rabbits failed to show evidence of any active tuberculosis, the tissues appearing normal and showing healed tubercles or, at the worst, the persistence of wandering cells in the stroma. However, after cessation of treatment, there was a relapse in 1 rabbit after a further period of thirty-four days, and in transmission experiments the extracts of the uveal tracts from the diseased eyes were infectious in 3 rabbits. The incubation period was definitely longer than that for the control transfers. Cultures of the uveal extracts were negative for tubercle bacilli in 5 instances and showed only a microscopic growth in the remaining culture.

The findings indicate that streptomycin has a definite bacteriostatic and a partial bactericidal action against the tubercle bacillus in ocular tuberculosis. The combination of streptomycin and "promizole" has a more pronounced clinical and a decidedly greater bactericidal action than has either agent used separately.

The therapeutic and the bactericidal action obtained from the combination of streptomycin and "promizole" appears somewhat greater than would be expected from a summation of their individual actions.

Johns Hopkins Hospital.

## ABSTRACT OF DISCUSSION

DR. PHILLIPS THYGESON, San Jose, Calif.: The difficulties encountered in clinical therapeutic research in ocular tuberculosis are serious but, when interpreted in the light of preliminary animal studies, are not insurmountable. Studies on human subjects are limited by many factors: 1. There is the difficulty in making a certain diagnosis of the disease—as a matter of fact, the diagnosis must always be presumptive, even in cases of frank granulomatous uveitis. 2. The series is necessarily small unless cooperative studies in several institutions can be undertaken. 3. Variability in the clinical course of human ocular tuberculosis makes necessary a large series for reliable interpretation of results. 4. It is impossible to control human results by histologic or cultural methods, as can be done in animal experiments. For these reasons, I look on the present study as being far more significant than the usual type of limited clinical therapeutic study of ocular tuberculosis.

When I was in Baltimore recently, I had the opportunity of examining with Dr. Woods representative animals from each of the three groups. The contrast between the gross appearance of the eyes in the control group and that of the eyes in group 3 was striking. I was especially impressed by the histologic evidence of differences between these two groups, which was clearcut and unmistakable. Dr. Woods has ample evidence to support his conclusion that "promizole" combined with streptomycin exerts a definite, if not complete, bactericidal action on the tubercle bacillus in the rabbit eye, and that the combination is superior to streptomycin alone.

These experiments would seem to be a guide to further therapeutic studies of ocular tuberculosis, since it is inevitable that chemotherapeutic agents more active than "promizole" and antibiotics more active than streptomycin will be developed in the future. I am informed that a considerably more active antibiotic, known as "aureomycin," is already in production. It seems to me that human therapeutic studies can now be undertaken with much more confidence and their results interpreted in the light of experience with these more exact animal studies.

I hope that the authors will offer a few words of recommendation to those of us who have begun human therapeutic studies with streptomycin and other agents, and I should like to ask whether they think that cooperative studies might be feasible in some of the larger cities. I have in mind the situation in San Francisco, where a program and clinic for the study and treatment of uveitis has been established at the University of California and patients are received from over the entire Bay area. It is conceivable that all patients with this disease, at least of clinic status, might be channeled to one institution, which could thus carry on extensive therapeutic studies with a sufficiently large series.

The problem of ocular tuberculosis, while not so important as it was twenty years ago, is still a major one, and it would seem from Dr. Woods's results that there is real hope of controlling this serious disease.

DR. JOHN G. BELLOW, Chicago: This excellent report is a continuation of the brilliant investigations which have added so much to knowledge of ocular tuberculosis.

This paper is important, for it destroys the old idea that ocular tuberculosis is basically any different from other infectious diseases of the eye. Although ocular tuberculosis differs from other infections

of the eye in many respects, it is essentially similar; of particular importance is the fact that it responds favorably to chemotherapeutic and antibiotic agents.

This paper demonstrates the value of the synergistic, or additive, action obtainable by using antibiotics in combination with chemotherapeutic agents and drugs. It has been shown that the effect of penicillin combined with the sulfonamide compounds, or of streptomycin with penicillin and the sulfonamide drugs, was far superior to the effect which might have been expected from each drug given separately.

The importance of early treatment has been stressed. At Northwestern University, Dr. Farmer and I have also demonstrated that streptomycin must be employed early in order to be effective in experimental and clinical infections of the eye. For example, infections of the vitreous produced by inoculating a virulent strain of streptococci can be prevented if streptomycin is injected intraocularly within twelve hours. If given later, it has little effect on the course of the infection.

While one cannot carry over the results from experimental animals to clinical cases without many reservations, we have reason to expect from Dr. Woods's experiments that effective results may be possible from the synergistic, or additive, effect of streptomycin and "promizole" given in smaller doses than would be employed when either agent is used alone. This reduces the chances of producing the toxic manifestations of both the antibiotic and the sulfone.

DR. ALAN WOODS, Baltimore: I should like to thank Dr. Bellows for his suggestion about the possible basic action of the sulfonamide drugs. It had not occurred to me. Dr. Thygeson brings up the fascinating question of the clinical use of these preparations and asks for certain information. The difficulty in their clinical use is based on two fallacies: 1. The diagnosis of ocular tuberculosis, as Dr. Thygeson said, is a presumptive one, and is usually about as good as the individual physician's experience with ocular tuberculosis. The validity of the diagnosis is also in proportion to his diagnostic equipment—his ability to rule out various factors. 2. The evaluation of the treatment is simply the personal opinion of the observer that the eye responded more quickly than would otherwise have been expected. Thus, the clinical therapeutic experiment is totally uncontrolled. The experiments I have presented are controlled; we can evaluate every factor. Therefore I think that in the clinical use of streptomycin and "promizole" in treatment of ocular tuberculosis it is necessary in the beginning to limit the use of the therapy to a condition so frankly ocular tuberculosis that there could be little doubt as to the diagnosis. Second, as to the dosage of streptomycin, there have been a number of interesting studies, largely from the Veterans Administration and the Fourth Streptomycin Conference. These studies indicate that people do just as well on 0.5 Gm. of streptomycin given twice a day as they do on 2 or 3 Gm. a day; in fact, the drug may be given only once a day, or every second day, with almost equally good effects. We have treated a number of patients with clinical ocular tuberculosis. The results must be the subject of another report when sufficient material is accumulated and when conclusions appear valid enough. We have given 0.5 Gm. of streptomycin intramuscularly twice a day. This dose would theoretically produce minor involvement of the vestibular nerve in a small percentage of cases. We

have had no trouble yet on this score with such a dose. Streptomycin has been given with the idea of continuing its administration until the patient has received a total of 100 or 125 Gm.; this represents about three months' treatment. "Promizole" can be given safely up to about 6 Gm. a day, 1.5 Gm. being given in four doses throughout the day. The total daily dose has sometimes reached 12 or 14 Gm. I am not now specifically recommending this form of treatment; I am only trying to answer Dr. Thygeson's question. I am afraid one might get into trouble if such treatment were used promiscuously. Because the physician's evaluation is about as good as his experience, I should like to see the use of these preparations limited, at first, to frank cases of ocular tuberculosis. I believe antibiotic and sulfonamide therapy has definite promise for this disease. I quite agree that better antibiotics will be found, and likewise better sulfonamide compounds. Others are now available. However, it takes about a year to carry out a study on one of these drugs and to evaluate the treatment in experimental animals.

I trust, therefore, that, if the treatment is used, it will be confined to cases in which there can be little, or no, question of the diagnosis and in which the outcome can be fairly well evaluated by an experienced ophthalmologist.

# RETINAL TUMOR ASSOCIATED WITH NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

Report of a Case

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IN 1882 von Recklinghausen<sup>1</sup> described a disease which he called neurofibromatosis. The disease is usually familial, showing mendelian dominance in successive generations, although occasionally skipping a generation. There is no sign of sex-linked inheritance. The disorder is characterized by cutaneous pigmentation and multiple tumors of the cranial and peripheral nerves. In some cases neurofibromatosis is associated with involvement of the skeleton and with disturbances of the glands of internal secretion and mental disorders, including epilepsy. The skin may show a uniform bronzing of various parts. The most typical cutaneous lesions are the circular or oval patches, with sharply defined edges, observed on the trunk. Nevoid formations are frequent.

An ocular complication described by Michel<sup>2</sup> (1873) before the syndrome itself was known was a tumor of the optic nerve in a girl with elephantiasis neuromatodes, a form of neurofibromatosis. At present the ocular complications of neurofibromatosis are classified in three sharply separated groups, each presenting interesting features and problems.

1. Tumors of the ocular adnexa and external coats of the eye. There may be hyperplasia and hypertrophy of the skin of the eyelids and the neighboring temporal and facial regions to a degree suggesting elephantiasis. Large or small, single or multiple tumors of the eyelids and the supraciliary region may be seen, as well as tumors of the palpebral and bulbar conjunctiva and of the cornea. Ptosis may be present. In 1945 Allende<sup>3</sup> reviewed the literature and reported an additional case of conjunctival tumor associated with neurofibromatosis.

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From the service of Dr. E. B. Gresser, Department of Ophthalmology, Beth Israel Hospital.

1. von Recklinghausen, W.: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuomen, Rudolf Virchow Festschrift, Berlin, 1882.

2. Michel, J.: Ueber eine Hyperplasie des Chiasma und des rechten n. opt. bei Elephantiasis, Arch. Ophth. **19**:145, 1873.

3. Allende, F. P.: Diffuse Neurofibromatosis (von Recklinghausen's Disease) Involving the Bulbar Conjunctiva, Arch. Ophth. **33**:110 (Feb.) 1945.



2. Defects of the bony structure of the orbit, causing pulsation of the eyeball. Dehiscences in the orbital roof allow free communication between the orbit and the intracranial cavity. Exophthalmos, which is frequently found with these orbital defects, may be caused either by orbital tumor formation or by herniation of brain tissue into the orbit. Pulsation of the eyeball is synchronous with the radial pulse. It is unaccompanied with bruit, and the patient is not annoyed by the condition. It was first reported by Rothcliffe and Parsons,<sup>4</sup> but received little attention until 1931, when Moore<sup>5</sup> reported 4 cases. In 1936 Wheeler<sup>6</sup> analyzed the condition and added 5 cases. Recently a review of the 20 reported cases, with the addition of 5 of their own, has been published by Peyton and Simmons.<sup>7</sup>

3. Intraocular tumors. For practical reasons, these may be subdivided into three groups. (a) Tumors of the uveal tract. They are especially interesting as a frequent cause of buphthalmos. Since Schiess-Gemuseus<sup>8</sup> (1884) described the first case, 33 such cases have been recorded in the literature. The most recent and thorough analysis is that of Anderson.<sup>9</sup> (b) Tumors of the optic nerve head. The first instance of a relation between ocular complications and neurofibromatosis is that of a tumor of the optic nerve head reported by Michel, as previously noted.<sup>2</sup> In 1940 Davis<sup>10</sup> tabulated 33 cases from the literature and added 5 cases of his own, all associated with neurofibromatosis. He suspected that other cases of reduced vision and optic nerve atrophy fall within this classification. (c) Tumors of the retina. This complication is extremely rare. Van der Hoeve,<sup>11</sup> in his painstaking researches on tuberous sclerosis, became convinced that this disease is closely related to neurofibromatosis, and he made ophthalmoscopic examinations in a great number of cases of these diseases. He was able to find retinal changes in 3 patients with neurofibromatosis. The first was a man aged 33 with bilateral tumor of the acoustic nerve and cutaneous lesions.

4. Rothcliffe, W. C., and Parsons, J. H.: *Plexiform Neuroma of the Orbit*, Tr. Path. Soc., London **55**:27, 1913.

5. Moore, R. F.: *Diffuse Neurofibromatosis with Proptosis*, Brit. J. Ophth. **15**:272, 1931.

6. Wheeler, J. M.: *Pulsation of the Eyeball Associated with Defects in the Wall of the Orbit*, Bull. Neurol. Inst. New York **5**:476, 1936.

7. Peyton, W. T., and Simmons, D. R.: *Neurofibromatosis with Defect in Wall of Orbit*, Arch. Neurol. & Psychiat. **55**:248 (March) 1946.

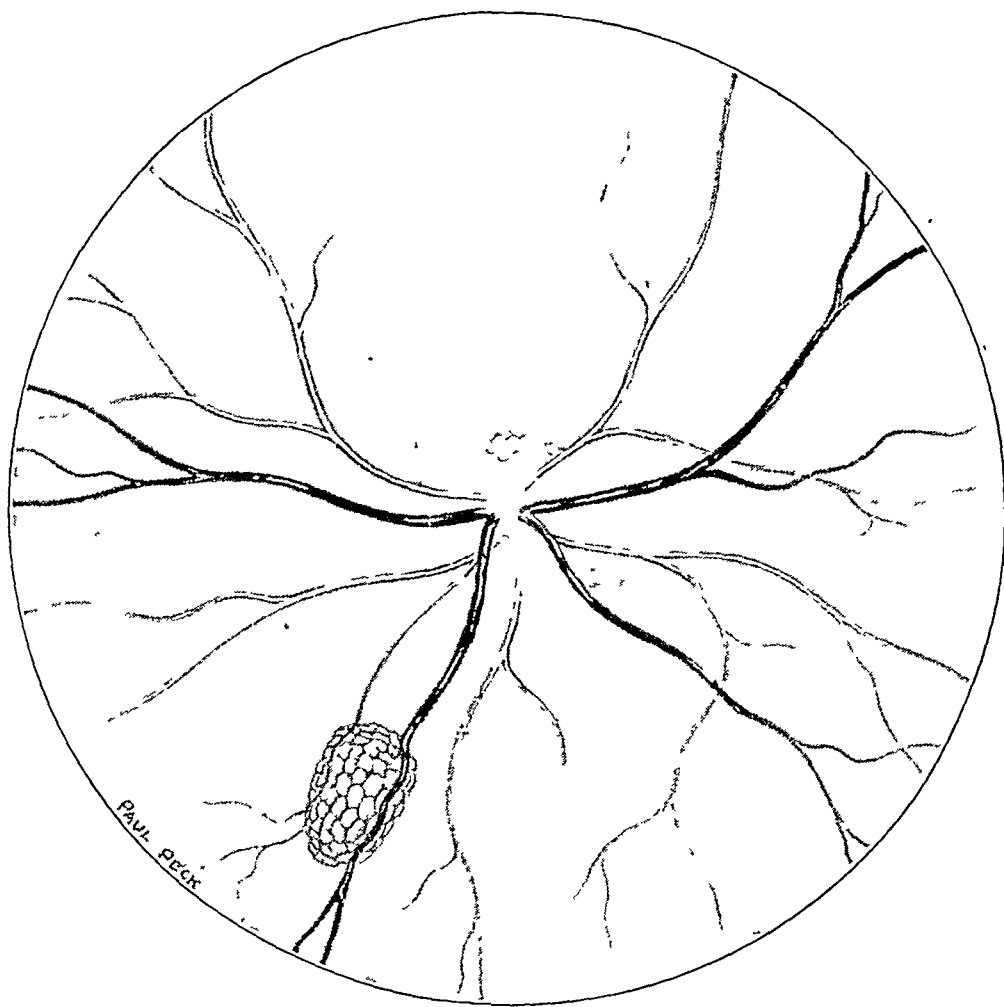
8. Schiess-Gemuseus: *Vier Fälle angeborener Anomalie des Auges*, Arch. f. Ophth. **30**:191, 1884.

9. Anderson, J. R.: *Hydrophthalmia or Congenital Glaucoma*, London, Cambridge University Press, 1939.

10. Davis, F. A.: *Primary Tumors of the Optic Nerve: A Phenomenon of Recklinghausen's Disease*, Arch. Ophth. **23**:734 (April) 1940.

11. van der Hoeve, J.: *Eye Diseases in Tuberous Sclerosis of the Brain and in Recklinghausen's Disease*, Tr. Ophth. Soc. U. Kingdom **43**:534, 1923.

In the macula of the left eye a small yellowish lesion and, below that, a grayish one were observed. Temporal to the nerve head was a grayish, umbilicated tumor. Another tumor was seen nasally and above between two vessels. The second patient presented a great number of grayish white tumors in each fundus. The third showed bilateral optic nerve atrophy and in the right eye several small tumors of the retina. The tumors closely resembled those seen in tuberous sclerosis. In 1938 Stallard<sup>12</sup> described the case of a youth aged 19 whose left eye showed



Fundus showing retinal tumor associated with neurofibromatosis.

a hemispherical, grayish mass protruding from the nerve head. The pathologic examination of the enucleated eye showed that the tumor had invaded all the layers of the retina and the advancing edge had wedged itself laterally between the nuclear layers. Whether the tumor in this case may be counted as an actual retinal tumor is doubtful. An additional case is reported from my experience.

12. Stallard, H. B.: A Case of Intraocular Neuroma (von Recklinghausen's Disease) of the Left Optic Nervehead, *Brit. J. Ophth.* **22**:11, 1938.

## REPORT OF CASE

S. R., a man aged 69, Jewish, sought advice from the clinic of Beth Israel Hospital on Feb. 8, 1938, because of pains in his legs. His low intelligence made the taking of an exact history difficult, but it was established that he was a widower with a healthy grown son and that his wife had not had any miscarriages or stillbirths. In 1915 a preliminary iridectomy had been performed on each eye. By 1927 the right eye was in a state of absolute glaucoma and was subsequently removed. Unfortunately, all previous records and specimens were lost.

Physical examination showed a slightly obese man, 5 feet 3 inches (160 cm.) in height and weighing 160 pounds (72.6 Kg.). The urine contained 110 mg. of sugar per cubic centimeter, and the blood sugar measured 190 mg. per hundred cubic centimeters. The internal organs were otherwise normal. The diabetes was easily controlled by diet. Beneath the skin around both elbows were numerous firm tumors, ranging in size from that of an almond to that of an egg. There was a fist-sized, soft tumor just below the sternum. Almond-sized angiomas were found near the upper lip and below the right scapula. Small, wartlike tumors were scattered over the trunk.

Examination of the eyes showed a fairly well fitting prosthesis in the right orbit. No tumor could be felt. The left eye was in normal position and moved normally. The conjunctiva and cornea were normal. The otherwise normal iris showed a surgical coloboma at 12 o'clock. A cataractous lens had been removed intracapsularly, leaving a clear pupil. The optic nerve was white, and the nasal margin slightly scalloped and irregularly raised, as in the presence of small drusen. At 12 and at 7 o'clock, finger-like areas of choroidal atrophy projected from the disk into the fundus. Below the macula and about 4 disk diameters distant from the optic nerve there was a grayish tumor, measuring 1 disk diameter in width and about 3 disk diameters in length. At its highest point its surface was raised 1 D., and it showed several whitish spots on its irregular surface. Vision with correction was 20/100. Tension was normal. Several attempts to evaluate the visual field were unsuccessful.

The diagnosis of melanoma was made and confirmed by the roentgenologic report of "osteoplastic metastasis involving the skull and the left side of the pelvis." The presence of metastases made the removal of an only eye in an elderly patient inadvisable. The patient remained under observation; the tumor did not grow, and in 1941 the diagnosis was changed to retinal tumor associated with neurofibromatosis. The last examination, in February 1947, showed the same picture as in 1938.

## COMMENT

The retinal tumor observed in this case of neurofibromatosis shows the same ophthalmoscopic picture as that of tumors seen in tuberous sclerosis. Whether the two diseases are identical is questionable, but a relationship has been suggested. As early as 1912, long before the retinal changes in either disease were known, Orzechowski and Novicki<sup>13</sup> drew such a conclusion from their pathologic studies. Van der Hoeve,<sup>14</sup>

13. Orzechowski, K., and Novicki, W.: Zur Pathogenese und pathologischer Anatomie der multiplen Neurofibromatose und der Sklerosis tuberosa (Neurofibromatosis universalis), *Ztschr. f. d. ges. Neurol. & Psychiat.* **11**:237, 1912.

14. van der Hoeve, J.: Eye Diseases in Tuberose Sclerosis of the Brain and in Recklinghausen's Disease, *Tr. Ophth. Soc. U. Kingdom* **43**:534, 1932; footnote 11.

who studied the condition most extensively from the ophthalmologic viewpoint, expressed the belief that tuberous sclerosis is closely related to Recklinghausen's neurofibromatosis, von Hippel-Lindau angiomatosis and the Sturge-Weber syndrome. The common point in these syndromes is the combination of cutaneous lesions with a tendency to form tumors in the most varied parts of the body, including the eye. He called the whole group phakomatosis, from the Greek word φακός for lentil, or mother spot. As long as the cause of these diseases is unknown and pathologists disagree about the nature and structure of the tumors, this is an excellent working hypothesis, and one cannot accumulate too much clinical and pathologic material to help in clarifying the situation. The importance of a thorough knowledge of these conditions in the everyday practice of ophthalmology is illustrated by our case, in which only a chain of circumstances saved the patient's eye from well intended, but unnecessary, enucleation.

#### SUMMARY

A retinal tumor in a case of neurofibromatosis (Recklinghausen's disease) is reported. The tumor is ophthalmoscopically identical with tumors commonly seen with tuberous sclerosis. In nine years of observation the fundus picture has not changed.

# VISION IN STRABISMUS

A Preliminary Report

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AND

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MUCH has been written about the effect of strabismus on vision, and since the time of Claude Worth<sup>1</sup> poor vision as a result of disuse in strabismus has been increasingly recognized. Since this time, also, less emphasis has been placed on the effect of vision on strabismus. It is our purpose to point out certain things in the relationship of vision and squint.

Little need be said about the fact of amblyopia ex anopsia. It is now well established that most visual defects associated with squint are the result of the squinting and subsequent disuse of the affected eye. Prior to Worth it was generally felt that there was much organic visual defect—congenital amblyopia—and that the squint resulted from the poor vision. In this paper, a portion of our file of private cases of strabismus will be analyzed. The factors in determination of vision in children will be commented on. The factors in the causation of amblyopia ex anopsia, as well as those factors which influence the treatment of amblyopia, will be discussed. The types and specific application of the various forms of treatment will be considered. Further, the association of organic ocular defect and strabismus will be commented on. It is not intended that this study should be exhaustive or conclusive; rather, it is felt that attention shall be drawn again to “how seeing affects squint” and “how squint affects seeing.”

## REVIEW OF THE LITERATURE

Brief reference to the literature reveals certain facts. Chavasse<sup>2</sup> graphed visual development in the child, showing that vision of 6/12 is normal for the 2 year old child and that vision matures gradually

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Read at a meeting of the Detroit Ophthalmological Society, Feb. 28, 1947, and the Washington, D. C., Ophthalmological Society, March 4, 1947.

1. Worth, C.: Squint, ed. 6, Philadelphia, P. Blakiston's Son & Co., 1929.

2. Chavasse, B. F.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940, chap. 26.

until, at the age of 5 years, normal vision of 6/7 is attained. It is recognized, however, that in some children vision of 6/6 is attained by the age of 4 years, and in others not until the age of 8, in eyes which are structurally normal.

Vision in the small child can best be determined by his ability in foveal fixation. Peter,<sup>3</sup> Worth<sup>1</sup> and Bielschowsky<sup>4</sup> agreed that foveal fixation is quickly lost in the infant and is quickly regained, and that the older child loses fixation more slowly and regains it more slowly. Whereas Worth<sup>1</sup> stated that foveal fixation cannot be regained after the sixth year of life, Bielschowsky<sup>4</sup> cited cases of adults who had extremely poor vision in a squinting eye until the good eye had been lost by injury or disease; then foveal fixation was regained, and in a few cases good vision was restored. Yoxall<sup>5</sup> cited 42 cases of patients, ranging in age from infancy to 11 years, all of whom regained foveal fixation and good vision on total occlusion for periods up to twenty-eight months. While the wisdom of such prolonged occlusion may be questioned, the final good vision seems justification in itself. No reference has been found to an attempt to correlate the ability in foveal fixation with an accurate estimate of visual acuity.

The fact of suppression as a forerunner to amblyopia ex anopsia is well established by the writings of Peter,<sup>3</sup> Travers,<sup>6</sup> Bielschowsky,<sup>4</sup> Enos,<sup>7</sup> Sugar<sup>8</sup> and others. Peter expressed the belief that the scotoma of suppression is only 2 to 3 degrees in diameter, while Travers and others mapped much larger scotomas. There are two scotomas in many cases of squint: the first, the area of the squinting eye which corresponds to the visual direction of the fovea of the fixing eye; the second, the area involving the macula of the squinting eye, and that only in cases of monocular squint. This is the forerunner of amblyopia ex anopsia (Travers<sup>6</sup>). Sugar<sup>8</sup> suggested the term "suppression amblyopia" as a better term than amblyopia ex anopsia. Enos<sup>7</sup> found that, while amblyopia is commonest with esotropia, suppression alone is commonest with exotropia.

Amblyopia ex anopsia, now recognized since its definition by Worth<sup>1</sup> in 1903, raises many questions. Bielschowsky<sup>4</sup> asked why some persons

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3. Peter, L. C.: *Extraocular Muscles*, ed. 2, Philadelphia, Lea & Febiger, 1936.

4. Bielschowsky, A.: *Lectures on Motor Anomalies*, Hanover, N. H., Dartmouth College Publications, 1940.

5. Yoxall, I.: Loss of Central Fixation, *Brit. Orthoptic J.* **1**:15, 1939.

6. Travers, T. a'B.: Concomitant Strabismus, *Brit. J. Ophth.* **20**:407, 1936.

7. Enos, M. V.: Suppression and Amblyopia, *Am. J. Ophth.* **27**:1266 (Nov.) 1944.

8. Sugar, H. S.: Suppression Amblyopia, *Am. J. Ophth.* **27**:851 (May) 1942.

with squint retain and others lose vision, and why the reduced vision is maintained indefinitely in spite of further disuse. Chavasse<sup>2</sup> stated that nearly 50 per cent of persons with esotropia are anisometropic and that the amblyopia varies directly with the anisometropia. He further classified amblyopia as of four grades, in two of which fixation is lost and even light projection is questionable, especially in the temporal field. In the third grade, eccentric fixation is present, and in the fourth foveal fixation and visual acuity up to 6/6 may be found. Feldman and Taylor<sup>9</sup> stated that ametropia is no great factor in causing amblyopia and that the higher refractive errors do not make the amblyopia harder to cure. Morgan<sup>10</sup> reported 77 cases of amblyopia in the Army, in 56 per cent of which it was associated with squint and presumably could have been prevented. Anisometropia was the cause in 30 per cent, and amblyopia without obvious cause was present in 14 per cent.

All authors, in discussing amblyopia ex anopsia, have emphasized the necessity of early treatment. Treatment consists primarily in occlusion. Morgan<sup>10</sup> cited Zimmerman as stating that 91 per cent of 68 patients obtained 20/20 + vision, while Yoxall<sup>5</sup> reported that prolonged occlusion led to 41 of 42 patients' regaining foveal fixation, and that 37 obtained equal vision in the two eyes after occlusion for periods up to twenty-eight months. Travers<sup>6</sup> stated that the prognosis depends on the age of the patient and the duration of squint. He cited Sattler, whose 89 patients obtained equal vision in two eyes—in children below 2 years in one to six weeks, in the 2 to 4 year group in one to three months and in the 8 to 12 year group in one to three years. He stated that a patient with amblyopia over 6 years of age with a vision of 6/60 or less has a poor prognosis. Worth<sup>1</sup> stated that the vision of 165 patients who had squinted less than one eighth of their lives improved to 6/6 on occlusion. Chavasse<sup>2</sup> stated that "expectation for sight for the amblyopic eye depends on the answer to two questions, 'How old was the patient when dissociation (failure of binocularity) began?' and 'How old is the patient now?'"

These references emphasize the uniformity of the acceptance of the origin of amblyopia from disuse, the necessity of early treatment for good results and the importance of total occlusion in order that the treatment be truly effective.

#### PRESENT STUDY

In the present survey are analyzed the data on 407 unselected private patients with squint, all of whom we examined. Throughout the analysis and discussion,

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9. Feldman, J. B., and Taylor, A. F.: Obstacle to Squint Training: Amblyopia, *Arch. Ophth.* 27:851 (May) 1942.

10. Morgan, G. E.: Amblyopia ex Anopsia in the Army, *Am. J. Ophth.* 29: 713 (June) 1946.

emphasis is placed on the ways in which the squint affected the vision and how the vision may have affected the squint. Patients having organic ocular defects are considered separately and are not necessarily considered unacceptable for treatment. Information obtainable from the history is analyzed and correlated with the clinical findings. The visual acuity is correlated with other ocular findings, such as the type of squint, the amount of deviation and the refractive error. Methods of treatment of amblyopia are indicated.

In this survey, corrected vision of 20/40 or less is considered subnormal and is assumed to be due to amblyopia ex anopsia unless an organic lesion could be demonstrated. The child knowing his alphabet was tested with the Snellen letter chart, while the child from 4 to 7 years of age was tested with the E chart. Below the age of 4 years, or until such an age as the E chart could be used, "fixation" was used to estimate vision. "Picture" charts were not used at any time, since too much depends on the child's previous experience with the objects being pictured.

During a routine examination of a squinting patient, the ability to fixate with each eye separately was noted, and, when possible, an estimation of visual acuity on the letter or the E chart was obtained at the same time. With this procedure, estimates were obtained for 222 eyes. Three grades of fixation were used: grade 1, good and central; grade 2, poor but central (or unsteady but central), and grade 3, eccentric or roving.

Table 1 shows that 178 eyes had "good and central" fixation. On the Snellen chart the visual acuity ranged from 20/15 to 20/200, with an average of 20/34. Thirty-one eyes had "poor and central fixation," with a range in acuity of 20/30 to 4/200 and an average of 20/165. Thirteen eyes had "roving or eccentric" fixation, with a range of 20/200

TABLE 1.—*Estimation of Visual Acuity by Foveal Fixation*

Fixation	Number of Eyes	Average Visual Acuity	Range of Visual Acuity
Good and central.....	178	20/ 34	20/ 15 to 20/ 200
Poor but central.....	31	20/165	20/ 30 to 20/1,000
Eccentric; no fixation.....	13	20/573	20/200 to 20/1,400

to 3/200 and an average of 20/573. It must be admitted that too few eyes in the last two grades were examined, and the findings are only suggestive. None the less, the "average" visual acuities have been substituted in the survey for the corresponding ability to fixate.

Of 407 patients with squint (table 2), 316 had a convergent squint; and, of these, 132 (41.5 per cent) were amblyopic; 86 patients had a divergent squint, with 14 (16.2 per cent) amblyopic, and 45 patients had squint with a predominant vertical element, 20 (30.8 per cent) of whom were amblyopic. The total number of amblyopic patients was 143, or 35.1 per cent. It is readily apparent that esotropia is associated with the greatest number of amblyopic eyes and exotropia with the smallest number, with squint with a vertical element holding an intermediate position.



What help may be obtained from the history regarding the effect of the squint on vision in these 407 patients? It is recognized that a parent's estimate of the age of onset of the squint, its constancy and whether it is alternating or monocular is often not reliable, but may be of some help. Data on the following points in the history were noted: type of squint (periodic or constant, monocular or alternating), age of onset, duration of the squint, existence of squint among near relations and, finally, visual "confusion" associated with the squint.

Of 393 patients (table 3) a history of "periodicity" of the squint was obtained for 181; and, of these, 32 (17.7 per cent) were amblyopic.

TABLE 2.—*Type of Squint in Relation to Amblyopia*

	Number of Patients	Amblyopic Patients	
		Number	Percentage
Convergent.....	316	132	41.5
Divergent.....	86	14	16.2
Vertical component.....	45	20	30.8
Totals.....	407	143	35.1

TABLE 3.—*Relation of Vision to History of Squint*

	Number of Patients	Amblyopic Patients	
		Number	Percentage
Type			
Periodic.....	181	32	17.7
Constant.....	212	113	53.3
Alternating.....	105	14	13.3
Monocular.....	288	131	45.5
Age of onset			
Nonamblyopic patients.....	1 yr. 2 mo.		
Amblyopic patients.....	1 yr. 9 mo.		
Duration of squint			
Nonamblyopic patients.....	2 yr. 4 mo.		
Amblyopic patients.....	6 yr. 5 mo.		

The remainder, or 212 patients, had "constant" squint, 113 (53.3 per cent) of whom were amblyopic. "Alternating" squint was noted in the history of 105 patients, with 14 (13.3 per cent) amblyopic, while of 288 with a history of "monocular" squint, 131 (45.5 per cent) had an amblyopic eye. Again, although it is recognized that a parent's statement that a squint is "periodic" or is "alternating" may not be entirely true, the evidence is strongly in favor of finding a much lower percentage of cases of amblyopia among patients giving such a history and a much higher percentage among those giving a history of a "constant" or a monocular squint.

Again, the statement of age of onset may not be reliable. It is probable that in most cases the squint is present for weeks or months before the parents are cognizant of the fact, except possibly in cases of squint of acute or sudden onset. The present series seems to demonstrate (table 3) that the average age of onset of squint is earlier among nonamblyopic patients (1 year 2 months) than among amblyopic patients (1 year 9 months). These data are contrary to present teachings and common sense. It must be remembered that many nonamblyopic patients have congenital squint which alternates, thus giving an early average age of onset for this group. Correction for this factor places the age of onset for the two groups at about the same level.

More significant figures (table 3), however, demonstrate the importance of the "duration" of the squint, that is, the period from the onset (as obtained from the history) to the time of the beginning of treatment. The average duration of squint for the nonamblyopic group was two

TABLE 4.—*Vision in Relation to History of Visual Confusion and to Familial History of Squint*

	Number of Patients	Patients with History of Confusion	Amblyopic Patients	
			Number	Percentage
Confusion				
Divergence.....	50	34	4	10.5
Convergence.....	128	51	18	35.3
Family squint				
Nonamblyopic patients.....				46.2
Amblyopic patients.....				52.4

years and four months, while that for the amblyopic group was six years and five months. It becomes evident that while the age of onset may not be of great significance, the longer the squint exists, the oftener amblyopia is found, and probably the more deeply seated it is and the more difficult to cure.

The obtaining of accurate data concerning the incidence of squint in the patient's family is notably inaccurate. In our series an effort was made to determine the incidence of squint among immediate relatives of the patient. It will be noted (table 4) that 46.2 per cent of nonamblyopic squinters had squinting relatives, whereas 52.4 per cent of amblyopic squinters had squinting relatives. The difference for these two groups does not seem significant.

A final group of facts obtained from the history has been little stressed by other investigators. It was noted by us that in a high percentage of cases of exotropia in children the parents' chief complaint was that the patient constantly closed one eye when in the bright light, and at times when looking intently at objects of interest. This "sign"

became sufficiently frequent that a tentative diagnosis of divergence excess was made whenever the history of "closing one eye in the bright light" (especially summer sunlight) was obtained. It was assumed that, while form suppression was adequate in cases of divergence excess during divergence, light suppression was inadequate and confusion took place. Actually, the history of transitory diplopia is not infrequent in cases of divergence excess, an observation which suggests that in these cases even form suppression is incomplete.

Stimulated by these thoughts, we took a careful history of symptoms suggesting visual confusion. Such signs as closing one eye, true diplopia, rubbing one eye (in the absence of other causes) and excessive clumsiness were noted. In the histories of 50 patients with exotropia, confusion was noted for 34, only 4 of whom had amblyopia (table 4). Of 128 patients with esotropia, 51 gave evidence of visual confusion, 18 of whom were amblyopic. The inference is twofold. Visual confusion occurs much oftener in cases of exotropia, and amblyopia is less frequent when evidence of confusion is present. The "confusion" is evidence of incomplete suppression, and amblyopia is less likely to be present.

More accurate evidence of the relationship of squint and vision may be obtained from the ocular findings than from the history. It was believed that (1) the type of squint (e. g., "mechanical," as opposed to accommodative, squint, or alternating, as opposed to monocular, squint), (2) the minimal deviation (e. g., the least squint of which the patient was currently capable in any circumstances) and (3) the size and dissimilarity of refractive errors in the two eyes might affect the visual acuity, or have affected it prior to the beginning of treatment.

The 407 patients (table 5) included 316 with convergent squint, 41.5 per cent of whom had an amblyopic eye. A breakdown of this group into cases of mechanical, accommodative and combined convergent squint gives additional information. Of 108 patients with mechanical convergent squint, 47 (43.5 per cent) were amblyopic. An interesting subgroup is congenital mechanical squint (sometimes called "pseudoparesis of the lateral rectus muscles," "bilateral paresis of the lateral rectus muscles" or "congenital paralysis of divergence"). This type is characterized by isometropia, early weakness of abduction and a tendency to alternate. Because of its frequent alternating character, amblyopia developed in only 29.4 per cent.

The group of 98 patients with accommodative convergent squint (table 5) contained 32 (32.6 per cent) with amblyopia. Patients with this type of squint may be divided into those with the "typical" form (persons having hypermetropia, with obvious squint before wearing glasses but straight eyes for distance and near vision with glasses), and

those with the "atypical" form (persons with low hypermetropia, with straight eyes for distance both with and without correction, but pronounced convergence for near vision both with and without correction). Of the 26 patients with "typical" accommodation, who had less opportunity for straight eyes before treatment, 11 (42.3 per cent) had amblyopia, whereas of the 35 patients with "atypical" accommodation, having straight eyes for distance at all times, only 5 (14.3 per cent) had

TABLE 5.—*Vision and Other Ocular Findings*

Type of squint	Number of Patients	Amblyopic Patients	
		Number	Percentage
Convergent.....	316	132	41.5
Mechanical.....	103	47	45.5
Congenital.....	34	10	29.4
Accommodative.....	98	32	32.6
Typical.....	26	11	42.3
Atypical.....	35	5	14.3
Combined.....	105	50	47.6
Monocular.....	239	120	50.0
Alternating.....	62	5	8.1
Divergent.....	86	14	16.2
Divergence excess.....	42	7	16.2
Convergence insufficiency.....	5	2	40.0
Combined.....	39	5	12.8
Monocular.....	75	10	13.3
Alternating.....	1	0	0.0
Minimal deviation, D.			
0 - 5.....	193	41	21.3
5 +.....	214	102	47.7
Refractive error			
Hypermetropia, D.			
0 - 1.....	77	18	24.9
1 - 4.....	225	77	34.2
4 +.....	71	39	55.0
Myopia.....	6	3	50.0
Astigmatism (2 + D.).....	41	23	68.3
Anisometropia, D.			
Less than 1.....	317	100	31.2
1 - 3.....	69	38	45.0
3 +.....	10	10	100.0

amblyopia. The cases are too few for a conclusive statement, but the inference is that the opportunity for binocular vision prevents amblyopia.

Of the 105 patients with "combined" convergent squint (some element of mechanical, as well as accommodative, convergence), 50 (47.6 per cent) had amblyopia (table 5). It is evident that in cases of convergent squint in which the eyes constantly are out of line amblyopia develops oftener than in the cases of periodic squint.

Also, it may be seen (table 5) that of 62 patients with "alternating" esotropia only 5 had any amblyopia (8.1 per cent). This diagnosis

was made at early visits, and at times amblyopia developed or became evident later. Of the 239 patients with monocular squint, 120 (50 per cent) had amblyopia, a figure corresponding closely to that for patients having a "history" of monocular squint.

Of 86 patients with exotropia (table 5), 14 (16.2 per cent) were amblyopic. Only 1 patient with alternating exotropia was found, the remainder being monocular. It should be recalled that many patients with divergence excess had "amblyopia," with a visual acuity of 20/25 or 20/30 +, but were not considered for this study.

In an effort to determine further the importance of the "opportunity for binocular vision" in inhibiting amblyopia, all patients were considered in the light of their minimal deviation. For instance, patients with divergence excess have straight eyes for near vision (a minimal deviation of zero), and patients with atypical accommodative convergent squint have straight eyes for distance (a minimal deviation of zero), whereas patients with mechanical and combined convergent squint never have straight eyes (a minimal deviation of 5 D. or more). Reference to table 5 shows that 193 patients had a minimal deviation of less than 5 D. and 41 (21.3 per cent) had amblyopia. The 214 patients with a minimal deviation of more than 5 D. included 102 (47.7 per cent) with amblyopia. It is then evident that the opportunity for binocular vision decreases the frequency of amblyopia.

A final correlation of interest is that of the state of the binocular refraction and its probable effect on corrected vision. It will be noted in table 5 that the hypermetropias have been subdivided into three groups on the basis of the size of the error. Myopia and excessive astigmatism are also indicated. The refraction of the eye having the larger error was used in each instance. Note that, contrary to the opinion of Feldman and Taylor,<sup>9</sup> who stated that ametropia is not a cause of amblyopia, the percentage of patients with amblyopia increased as the size of the hypermetropic error increased. Of 77 patients having an error of less than 1 D., 18 (24.9 per cent) were amblyopic, while of 225 patients having an error of from 1 to 4 D. 77 (34.2 per cent) were amblyopic and of 71 patients having an error of more than 4 D. 39 (55 per cent) were amblyopic. The increase in the percentage incidence of amblyopia as the hypermetropic correction increases is striking and rather conclusive.

Myopia occurred too infrequently (except as the congenital monocular and binocular types) to justify conclusions. Excessive astigmatism (over 2 D.) shows the highest percentage of patients with amblyopia (68.3 per cent), amblyopia occurring in 41 patients (table 5).

The role of anisometropia in the causation of amblyopia has been noted by numerous authors. In this study, it is evident that as the difference in the refractive error in the two eyes increases the percentage of cases

of amblyopia increases strikingly. Of 317 patients (table 5) having a difference of less than 1 D. in the two eyes, 100 (31.2 per cent) were amblyopic, whereas 38 of 69 patients (45 per cent) having a difference of 1 to 3 D. were amblyopic and all of 10 patients having a difference of 3 D. or more in the two eyes were amblyopic (100 per cent).

It is evident from consideration of the refractive errors of these patients with strabismus that as hypermetropia increases, or as anisometropia increases, amblyopia increases.

#### TREATMENT

Though numerous suggestions have been made concerning the treatment of amblyopia ex anopsia, the choice of effective procedures is limited. The purpose in such treatment is to force the use of the amblyopic eye, to create interest in such use and to encourage the patient in such activities by any methods possible.

When amblyopia is extreme (e. g., when there is loss of central fixation), total occlusion of the fixing eye is imperative. This can be



Various types of occluders. *A*, an elastoplast occluding pad; *B*, zinc adhesive tape fastened to the anterior surface of the lens; *C*, music-mending tape.

done only by means of (1) gauze pads held in place with adhesive isinglass tape, (2) pads held by a roller bandage or (3), most easily and effectively, by a prepared elastoplast (adhesive) occluding pad<sup>11</sup> (figure, *A*). I use one 2 by 3 inches in size and have the parent change it every second or third night unless it loosens sooner. Spectacle occluders or other types of occlusion attached to spectacles can be removed too easily by the patient and are not effective in the case of severe amblyopia. The small child (up to the age of 3 years) should return every seven to twenty-one days for an estimation of vision in each eye. I have seen 1 year old infants with no fixation in the right eye return after wearing an occlusion for two weeks with excellent fixation in the right eye and with no fixation in the left eye. The younger the patient, the more frequent the visits should be. Patients from the ages

11. These pads are manufactured under the name of "elastoplast coverlets" by Duke Laboratories, Inc., Stamford, Conn.

of 3 to 6 years may be seen not oftener than every six weeks, unless visits are necessary to boost the patient's morale and maintain interest. When the initial vision is less severely impaired, again the visits should be more frequent, since more rapid improvement may be expected.

As vision improves, foveal fixation becomes steady and the patient acquires an increased sense of security, the amblyopic eye should be stimulated by having the child do such things as tracing, drawing, cutting out paper dolls, threading beads, working puzzles and reading. The simple fact of occlusion may not stimulate the fovea as do these procedures, which require the effort to see better foveally.

Complete occlusion should be continued until vision of 20/70 or better is obtained. Then several methods of subtotal occlusion may be used. Plastic and rubber occluders which fit on the spectacle frame are

TABLE 6.—*Methods of Treatment of Amblyopia*

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Occlusion
A. Total occlusion
Adhesive pad
B. Subtotal occlusion
(a) Spectacle occluders
(b) "Built-up" patch
(c) Music-mending tape
(d) Music-mending tape with atropine
C. Blurring
(a) Several (?) hours per day
(b) Alternate days or weeks
Stimulation of vision
(a) Tracing, reading, paper dolls, etc.
(b) Movies
(c) Flashing lights (?)
Morale boosters
(a) Rewards
(b) Penalties

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useful. We have used chiefly two forms of subtotal occlusion. At times a large piece of zinc adhesive tape is fastened to the anterior face of the lens before the fixing eye, extending 1 inch (2.5 cm.) above the spectacle frame and well nasally, then being folded back on itself and fastened to the posterior surface of the lens. This gives effective occlusion of the lens, as well as above and nasally (figure, B).

More often the lens before the fixing eye is occluded by covering its posterior surface with music-mending tape (a translucent adhesive paper), through which light, but not form, may be seen (figure, C). This type of occlusion is not so obvious to the casual observer, and so it is not too unpleasant to the wearer. If the patient is inclined to peep over the spectacles, 1 drop of 0.5 per cent atropine sulfate should be instilled into the "occluded" eye daily. If any considerable degree of hypermetropia is then present, the blurred vision resulting from

atropinization discourages further attempts at peeping, and the patient is more inclined to use the nonoccluded (amblyopic) eye.

We have not used atropine alone for blurring, for several reasons. First, the hypermetropia must be considerable if atropine alone is to be effective. Second, the lack of occlusion makes the treatment of suppression and abnormal retinal correspondence less adequate. Third, light in the atropinized eye is annoying.

We have used clear nail polish, smeared or stippled on the lens before the fixing eye, as a finishing procedure. The patient who has 20/30 in one eye and 20/20 in the other will be encouraged by the presence of the substance to use the other eye but, at the same time, will have some opportunity for binocular vision. We have had much complaint of glaring of light through the polish, with subsequent confusion; so we use it infrequently.

As a finishing procedure, or to maintain vision in a previously amblyopic eye, we frequently use part time occlusion. In the patient who has vision of 20/20 — and a tendency to lose vision under orthoptic treatment, the vision may be maintained by use of music-mending tape for two to five hours in the evening while he is studying or reading. In this connection, it should be stated that the mere obtaining of good vision in the amblyopic eye offers no assurance that such vision will be maintained. Visual relapse is frequent, and during treatment the vision of each eye should be tested at frequent intervals.

A final comment on treatment of amblyopia should be made. The wearing of total occlusion by the small child, or of glasses occlusion by the older one, is not often accepted graciously. Rewards in the form of candy, extra movies or money must be offered. The "flat of the hand" must be used occasionally, but not if any other method will work. High praise must be heaped on the little patient if he wears his patch, and enthusiastic comment must be made about any small amount of visual improvement. The parents should understand that to the person with an amblyopic eye occlusion is the last court of appeal. The patient's false hopes that surgical intervention or "exercises" may cure the vision must be dispelled and the necessity of complete occlusion emphasized again and again. We feel that occlusion should be discontinued unless appreciable visual improvement can be shown after three months of conscientious effort. Treatment should be continued as long as improvement is evident. Often, the final vision is less than 20/20 even though the patient, the parents and the oculist have cooperated to the fullest. This is more likely to be true if the beginning of treatment was delayed or the initial vision poor. The best possible vision should be maintained until fusion and alinement have been gained, if possible.



## EFFECT OF VISION ON SQUINT

Most of this study has been devoted to "how squint affects vision." We should like to comment on how vision affects the position of the eyes.

Chavasse<sup>2</sup> stated that an eye blind at birth and in early infancy will turn out, an eye blind in later infancy and in childhood will turn in, an eye blind in adolescence will turn in less, an eye blind in early adult life will be about straight and an eye blind in later adult life will turn out. We have analyzed 29 cases of squint in which there were organic ocular defects to determine the position of the eyes and the visual defect.

These cases of organic ocular defects (table 7) include 4 of congenital cataract, 2 of coloboma of the optic disk, 5 of congenital nystagmus, 6 of Duane's retraction syndrome, 8 of congenital myopia (4 of

TABLE 7.—*Vision and Organic Defects*

	No. of Patients	Ortho- tropia	Exo- tropia	Eso- tropia	Ambly- opia
Congenital cataract (or aphakia).....	4	..	1	3	4
Coloboma of disk.....	2	..	1	1	1 (20/100 to 20/30)
Congenital nystagmus.....	5	..	..	5	3
Duane's (retraction) syndrome.....	6	3	1	2	1
Congenital myopia					
Monocular.....	4	..	2	2	3 (3/200 to 20/50)
Binocular.....	4	..	..	4	1
Congenital ptosis.....	1	..	1	..	0
Congenital glaucoma.....	3	..	2	1	?
Chorioretinitis .....	2	..	..	2	2

monocular and 4 of binocular type), 1 of congenital ptosis (pupil not covered), 3 of congenital glaucoma and 2 of chorioretinitis. Of this group of 31 cases there was definite amblyopia in 15, and the patients either were not candidates for treatment or did not respond to treatment. The vision of 3 patients could not be determined with any degree of accuracy.

Certain of this group had sufficient opportunity for foveal vision in each eye to insure that vision would not suffer. Of 6 patients with Duane's syndrome, the eyes of 3 were orthophoric in the primary position, though obviously misaligned when abducting or adducting. Two had obvious esotropia, and 1 obvious exotropia, when the eyes were in the primary position. However, only 1 patient had amblyopia, for the other 5 had either spontaneous fusion or alternation.

Of 5 patients with congenital nystagmus (but with foveal fixation), 3 had amblyopia, and 2 of these were amblyopic in both eyes. There is some question whether mild foveal damage or the nystagmus was the

cause of the amblyopia. All 5 were esotropic and presented no opportunity for single binocular vision. Attempts at occlusion in cases of congenital nystagmus have been unsuccessful, largely because any type of covering of one eye causes a great exaggeration of the nystagmus, with accompanying confusion and annoyance. We feel that no treatment except the proper spectacles, or surgical intervention in cases of the severe squints, should be attempted.

One patient with congenital ptosis, with the lid margin just above the lower margin of the pupil, had no amblyopia because the opportunity for single vision was present part of the time. The squint was one of divergence excess.

Three patients with monocular congenital glaucoma seemingly have visual defects, but it cannot be determined whether this is due to the arrested glaucoma or to amblyopia ex anopsia or to both. Treatment with intermittent occlusion is being carried on. It is interesting that after the eye has been patched for two or three days these patients seem to become adjusted and are little inconvenienced in using the glaucomatous eye.

The 8 patients with congenital myopia fall into two groups. The 4 with bilateral myopia (with a myopia from 8 to 16 D.) were all esotropic, and only 1 was amblyopic. The 4 patients with monocular myopia had a high degree of myopia in one eye, and either slight myopia or moderate hypermetropia in the other eye. Two of these were exotropic and 2 were esotropic, and 3 of the group had extreme amblyopia in the myopic eye. One case is particularly interesting. A girl of 6 years was first seen with corrected vision of 3/200 in the right eye and 20/20 in the left eye. I did not encourage treatment, but the parents were insistent and the patient was cooperative. After nine months of continuous occlusion, vision in the right eye has improved to 20/50 + with a correcting lens of — 4.50 D. sph.  $\subset$  4.00 D. cyl., axis 180. The parents understand that the probability of single binocular vision is slight, but a "spare" eye having 20/50 + vision may some day be important to this patient.

Four patients with congenital cataract all had at least one amblyopic eye, though treatment was begun early. We have found it most difficult to preserve two seeing eyes when one or both are cataractous and have to be treated surgically.

Two patients with chorioretinitis involving the general macular region had poor vision in the involved eye, and attempts at occlusion were entirely unsatisfactory.

Two cases of coloboma of the disk are included. The patient with the severer involvement did not respond to treatment and remained amblyopic. Vision of the patient with the less severe involvement improved from 20/100 (corrected) to 20/30 after five months of continu-

ous occlusion, and this improvement has been maintained with several short periods of part time occlusion. It is interesting that this patient has acquired third grade fusion and has largely overcome a divergence excess. Results in the 2 cases (1 of monocular myopia and 1 of coloboma of the disk) just cited, as well as in several similar ones not included in this series (not occurring in the portion of the file analyzed for this paper), have convinced us that in some cases of organic defect of the eyes there is a superimposed amblyopia ex anopsia. Treatment should be tried in all cases, for at least three months, unless the imposed handicap is extreme and persists.

#### ADDITIONAL COMMENT

Certain miscellaneous observations are worthy of comment. We have constantly noted that an amblyopic eye would seem to have poor abducting power, and we earlier assumed that the lateral rectus muscle was parietic. More recently, having cured much of the amblyopia, we have noted that abduction becomes normal as visual acuity improves.

Further, we have frequently noted that a squinter with an amblyopic eye has primary and secondary deviation. In other words, when the "good" eye is fixing, the deviation is less; but when the amblyopic eye is fixing, the deviation is greater. We have assumed that more accommodative effort is exerted when the amblyopic eye is fixing and that this causes a greater convergence.

These two points illustrate ways in which vision affects the function of muscles.

Our methods of analyzing our results of treatment of amblyopia are unsatisfactory and the figures obtained inconclusive. It is hoped that in a further, more complete, study the results may be published.

#### SUMMARY

1. A series of 407 cases of squint is presented.
2. A method of determining visual acuity by ability in foveal fixation is suggested.
3. The incidence of amblyopia is correlated with certain facts obtained from the history of patients with strabismus.
4. The incidence of amblyopia is correlated with certain ocular findings (e. g., type of squint, amount of squint and binocular refraction).
5. The treatment of amblyopia ex anopsia is discussed.
6. The relationship of organic ocular defects and amblyopia ex anopsia is discussed.

#### CONCLUSIONS

1. Visual acuity can be estimated in the infant by determining the ability in foveal fixation.

2. The greater frequency of amblyopia in patients with strabismus can be predicted from a history of "constant," or "monocular," deviation.

3. While the average age of onset of squint may not be significant, the average duration of the squint before treatment is most significant in the production of amblyopia.

4. "Visual confusion" occurs more frequently with exotropia and suggests a less severe degree of amblyopia.

5. Amblyopia is more frequent with convergent than with divergent squint, and with mechanical convergent than with accommodative convergent squint, and is least frequent with alternating squint and with "atypical" accommodative convergent squint.

6. The incidence of amblyopia increases directly with the degree of hypermetropia or the degree of anisometropia present.

7. Total occlusion is the treatment of choice for amblyopia ex anopsia and can be obtained only by "face patching."

8. Amblyopia ex anopsia may occur as the result of organic ocular defects and can be improved in some cases with treatment.

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## CONICAL CORNEA AND MONGOLISM

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RECENTLY I had under observation 2 patients with bilateral conical cornea associated with mongolism, a man aged 22 and a woman aged 29; in the latter the conical cornea was complicated with cataract, commonly noted in older persons with mongolism. A perusal of the literature revealed as ocular symptoms of mongolism only nystagmus, convergent strabismus and blepharitis in some cases, in addition to the almost constant presence of the oblique palpebral fissure, with slanting of the lids up and temporalward and the epicanthus. A search of textbooks for mention of conical cornea associated with mongolism was futile; even such books as Tassman's,<sup>1</sup> when discussing ocular disturbances in conjunction with general systemic disease, failed to mention the occurrence of keratoconus. Conical cornea and mongolism are both anomalies, the nature of which is still a moot question.

Recognition of conical cornea is usually attributed to the observation of Taylor (1766); but Demours, in Paris, was actually the first (1747) to give an accurate description. Himly held the belief that the disease was a hyperkeratosis. The actual morphologic description was given by Wardrop (1819). R. Wagner's histologic examination revealed that the conical deformity depends on thinning of the central portion of the cornea, without the presence of inflammatory symptoms. In the majority of cases conical cornea is bilateral, to a variable degree; it affects female patients more often than male, and appears with and without rupture of Descemet's membrane. According to Stock, it is never congenital and appears usually after the age of 10 years; but experience has shown that often keratoconus is noted about the age of puberty, and there are rare instances of development at about the age of 40. The familial and hereditary tendencies suggest the possibility of a developmental disturbance, even though nothing is known of the nature of such a defect. Cases like Behr's,<sup>2</sup> in which conical cornea was associated with blue sclera and spontaneous luxation of various joints, are evidence in support of such an explanation, the develop-

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1. Tassman, I. S.: *The Eye Manifestations of Internal Diseases*, St. Louis, C. V. Mosby Company, 1942.

2. Behr, C.: *Beitrag zur Aetiologie des Keratokonus*, Klin. Monatsbl. f. Augenh. **16**:281, 1913.

mental disturbance being more probable in cases in which conical cornea is associated with anomalies of various parts of the external membrane of the eye. In the cases in which a congenital anomaly apparently is not responsible, acquired changes representing dyscrasic factors were considered by many authors, including Elschmig, who hypothesized a chronic inflammatory disease of the endothelium and Descemet's layer.

In Geyer's<sup>3</sup> series of 30 cases of mongolism, 2 cases of bilateral conical cornea (in males 28 and 13 years of age, respectively, sibships 14 and 21) were mentioned; in my limited material 2 other cases were seen. Since persons with mongolism are short lived and conical cornea usually develops about the age of puberty, the occurrence of conical cornea in cases of mongolism should not be considered a rare coincidence. In order to determine the significance of simultaneous occurrence of conical cornea and mongolism, I shall review present knowledge concerning the two conditions.

## MONGOLISM

### CLINICAL CHARACTERISTICS

The first description of mongolism was given by Down<sup>4</sup> in 1886, the term mongolism being chosen because of the Kalmic, or Tartar, type of the features. Crookshank<sup>5</sup> tried to explain the condition as due to crossing with persons of the mongoloid race. The presence of mongolism in various races and the absence of the condition in crossings of Chinese and white persons or of Chinese and Negroes is ample evidence of the invalidity of such an explanation.

Children with this type of mental deficiency show a flat, broad face; oblique palpebral fissures; short nose with broad, depressed bridge; short, sparse; brownish black hair, and small, rounded head. The type of idiocy is considered to be due to antenatal arrest in development (both physical and mental), characterized by brachycephaly, combined in later years with the type of physiognomy seen in members of the mongolian races. The brachycephaly, or shortening of the antero-posterior diameter of the skull, is the most constant and distinguishing feature. Not only is the skull distinctly round, but the occipital region is flattened and the occipital protuberance is absent. The plane of the occiput tends to be parallel with the plane of the face and forehead; the anterior, posterior and transverse diameters of the skull are nearly

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3. Geyer, H.: *Zur Aetiologie der mongolischen Idiotie*, Leipzig, G. Thieme, 1939.

4. Down, J. L.: *Observations on Ethnic Classification of Idiots; Clinical Lectures and Reports*, London Hosp. 3:259, 1866.

5. Crookshank, F. G.: *The Mongol in Our Midst: A Study of Man and His Three Faces*, ed. 3, London, George Routledge & Sons, Ltd., and Kegan Paul, 1931.

equal, and the fronto-occipital circumference is greatly diminished. Of 26 patients, Geyer found 16 hyperbrachycephalic, 8 brachycephalic and 2 dolichocephalic. The fontanels and cranial sutures show delayed closure. The face is round, and often depressed, with chubby cheeks. At birth the children are undersized and extremely weak; growth is slow; later the child is well nourished and fat, especially near puberty. Puberty is reached late; the pubic and axillary hair is sparse. In the girl, menstruation occurs late, is irregular and ceases early. The eyebrows tend to run upward and slightly outward. The zygomatic bones are prominent; the palpebral fissures are narrow and slope down and in. Convergent strabismus or nystagmus, or both, most commonly the strabismus, is present. Epicanthus is a frequent, though by no means a constant, feature. There is hypotonia not only of the muscles of the extremities but of the muscles in general, hence, the typical facial expression and frequent slight ptosis (possibly due to hypofunction of the adrenal glands). The mouth is small, round and constantly open; the lips are somewhat everted, especially the lower one, which is usually thicker than normal. The tongue is protruding; the most striking feature appears some time after birth; the papillae become enlarged; the surface shows deep and numerous fissures (scrotal tongue). Deformities of the palate are common, the chief type being V shaped. Dentition is much delayed, and the teeth are frequently very irregular; the second dentition occurs at the proper age, and the teeth are less irregular. Congenital heart disease is commoner than with any other type of idiocy. Spinal curvatures do not belong to the picture and, if present, are only secondary to the general muscular weakness. Ossification is much delayed; the hands are short, broad and stumpy. The fingers are round and thick and taper toward the extremities; the thumb and the little finger are shorter in proportion to the other fingers than normal. Clinodactyly, camptodactyly or syndactyly is frequent. Laxity of the joints is a prominent feature, with a greater range of mobility than normal; this is due to laxity of the ligaments or, more probably, to deficient tonicity of the muscles. Undescended testes, hernia, deformity of the ears and separation of the great toe are often noted.

Defects of intelligence are early observed; walking and speech are delayed until the third year; the vocabulary is later very limited; failure to form sentences is characteristic. The child remains idiotic; death occurs usually in the first year, as a result of respiratory, intestinal or other infections; the older child with mongolism is susceptible to tuberculosis. Mental deficiency ranges from the mildest form of imbecility to complete idiocy. During infancy, the disposition is one of apathy ("good child, easy to manage"); later, the child is characteristically good tempered, cheerful, affectionate, playful and a lively mimic, with musical and dancing ability. Development of walking and movements is generally delayed.

## ETIOLOGY OF MONGOLISM

Mongolism is characterized by generalized retardation of somatic, skeletal and mental development, in many instances resembling cretinism. Strange to say, the great Virchow was opposed to considering it a separate entity; he included it with the group to which congenital rachitis and sporadic cretinism belong. The former, congenital rachitis, is known as chondrodystrophia fetalis; similarly, myxedema and sporadic cretinism are entirely distinct from mongolism.

Evidence has been present that mongolism is associated with advanced maternal age. The development of mongolism has been said to be influenced by ill health in the mother, uterine exhaustion, increased amniotic pressure and defective nidation. In 56 per cent of Kreyenberg's<sup>6</sup> series of 50 cases the child with mongolism was the last born of the family; in 46.7 per cent the mother was 40 or older, and in about 50 per cent the mother was older than the father. Kreyenberg observed only 1 patient with mongolism in a family, but others have reported 2, 3 or even 4 such persons in the same sibship, an observation pointing to a certain functional depletion of the ovaries of the mother. The child with mongolism is often the last offspring of an older mother, but mongoloid children are born to young mothers as well—perhaps the first child, followed by normal, healthy children. According to Leeper,<sup>7</sup> 5 were first-born children; 90, last-born children, and 10 were the fifth or sixth in the sibship, followed by a premature infant or a stillbirth. Therefore, the correlation between maternal age and mongolism is not conclusive, and the theory of uterine exhaustion, postulated by Shuttleworth, does not explain the occurrence of children with mongolism who are born to young mothers. The possible role of defective nidation (development of endometrial epithelium in the intermenstrual period) was advocated by von der Scheer; accordingly, the local changes in the endometrium lead to poor developmental possibilities for the fertilized ovum. Extrauterine gestation, in which the placenta is attached in an unquestionably more undesirable location, producing, nevertheless, a living child free from mongolism, is against the possibility of this factor as a cause of mongolism. Space does not permit me to discuss other proposed, but less important, factors. Among these are alcohol; syphilis; previous frequent child bearing; toxic influences, leading to reproductive exhaustion; exhaustive illnesses during pregnancy; increased amniotic pressure; deficiency of vitamins and hormones during pregnancy (Tredgold),

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6. Kreyenberg, G.: *Der Mongolism*, in Bumke, O., and Foerster, O.: *Handbuch der Neurologie*, Berlin, Julius Springer, 1935, vol. 2.

7. Leeper, B.: *Mongols*, *Rev. Neurol. & Psychiat.* 10:11, 1912.



leading to alteration of chromosomes; ovarian damage, preventing the maturation of the ovum (Geyer); diminished secretion of progesterone (Penrose<sup>8</sup>), resulting in disturbance in the embedding of the fertilized ovum; fetal hyperthyroidism (Clark), and possible damage from previous abortions (curettage and roentgen irradiation, Engler<sup>9</sup>), all of which have been suggested as having a direct influence on the development of mongolism. The evidence on which these assumptions were based is scanty and unconvincing. The hereditary influence, change in the germ plasm and disturbances in the glands of internal secretion are the most important factors investigated during the past decades and, consequently, are of sufficient significance to be considered here.

*Endocrine Factors.*—The possibility of an endocrine genesis of mongolism is often discussed, with particular reference to disturbances of the thyroid and the pituitary gland. In the majority of cases in the older literature pathologic changes in the glands were absent; nevertheless, Gordon<sup>10</sup> expressed the belief that at times a functional disturbance of the thyroid is present in mongolism, independent of the presence of demonstrable manifestations of hypothyroidism or athyreosis. Kassowitz<sup>11</sup> expressed opinion was in agreement, that is, that persons with mongolism exhibit changes in the thyroid at times. Hill<sup>12</sup> reviewed the material from 20 autopsies on the thyroid gland in cases of mongolism. According to Wieland, the thyroid was observed to be normal on macroscopic and microscopic examination by most of the older authors; only a few noted the presence of hypoplasia and definite histologic changes and expressed the opinion that there was no evidence of the thyrogenesis of mongolism. Morphologic changes were described in 3 cases by Thomas and Delhougne.<sup>13</sup> An embryonic type of thyroid, with follicles and poor colloid content, was observed in a 3½ month old infant; the thyroid of a 21 month old child exhibited rich areas of colloid and others of embryonic type, with poor colloid substance; the thyroid of the third child, 8½ months of age, had abundant follicles but was still of undifferentiated tissue and poor colloid content. The authors considered the possibility that the changes were

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8. Penrose, L. S.: Relative Aetiological Importance of Birth Order and Maternal Age in Mongolism, *Proc. Roy. Soc., London*, s.B, **115**:431, 1934.

9. Engler, M.: Causation of Mongolism, *J. Neurol., Neurosurg. & Psychiat.* **7**:27, 1944; Causation and Prognosis of Mongolian Idiocy, *Proc. Roy. Soc. Med.* **38**:211, 1945.

10. Gordon, M. B.: Morphological Changes in the Endocrine Glands in Mongolian Idiocy, *Endocrinology* **14**:1, 1930.

11. Kassowitz, M.: Infantiles Myxödem, Mongolismus und Mikromelie, *Wien. med. Wchnschr.* **52**:1049, 1105, 1202, 1256, 1301, 1357, 1409 and 1452, 1902.

12. Hill, B.: Mongolism and Its Pathology, *Quart. J. Med.* **2**:49, 1908.

13. Thomas, E., and Delhougne, E.: Schilddrüsenbefunde bei Mongolismus, *Monatschr. f. Kinderh.* **28**:519, 1924.

normal, as the embryonic stage may still persist at this age. Fromm<sup>14</sup> considered the development of the thyroid gland in his case as insufficient for the age of the patient (18 months); Brudzinsky<sup>15</sup> described the thyroid in his case as rudimentary, and Bernheim-Karrer,<sup>16</sup> as partially sclerosed and atrophied. Bourneville<sup>17</sup> observed involvement of the thyroid gland in 2 cases. In the first case, the trabeculae were hypertrophied; the vessels were sclerosed, and interstitial hemorrhages, slight pigment and fatty infiltration were noted, with slight, but pathologic, modification of the elements of the gland. In the second case, the thyroid showed alterations in all its elements. The colloid material in the vesicles was almost completely replaced with cells derived from glandular epithelium; the vesicles were choked with these cells, and some were filled with fat; there was extensive sclerosis of the glands, and the trabeculae were thickened and infiltrated with young connective tissue. Oberthür and Phillipe<sup>18</sup> described slight interstitial proliferation about the capillaries and small hemorrhagic areas with pigmentation of the connective tissue; Lange<sup>19</sup> noted the presence of colloid degeneration with interstitial proliferation. Numerous authors (Kaufmann,<sup>20</sup> Meltzer,<sup>21</sup> Comby,<sup>22</sup> Thiemich,<sup>23</sup> Chartier,<sup>24</sup> Tilloy,<sup>25</sup> Cozzolino<sup>26</sup> and Sutherland<sup>27</sup>) did not observe changes in the thyroid in cases of mongolism.

14. Fromm, J.: Sektionbefunde bei einem Fall von Mongolismus, *Monatschr. f. Kinderh.* **4**:245, 1905.

15. Brudzinsky, J.: Contribution à l'étude du myxoedème infantile, du mongolisme et de la micromélie, *Arch. de méd. d. enf.* **11**:513, 1908.

16. Bernheim-Karrer: Ueber zwei atypische Myxödemfälle, *Jahrb. f. Kinderh.* **64**:26 and 746, 1906.

17. Bourneville: De l'idiotie mongolienne, *Arch. de neurol.* **16**:252, 1903.

18. Oberthür, J., and Phillipe, C.: Examen histologique de deux cerveaux d'idiot mongoliens, *Compt. rend. de Bicêtre* **3**:148, 1901-1902. Oberthür, C. R.: *Progrès méd.* **10**:44, 1904.

19. Lange, P.: Beiträge zur pathologischen Anatomie des Mongolismus, *Monatschr. f. Kinderh.* **5**:233, 1906.

20. Kaufmann, E.: *Lehrbuch der speziellen pathologische Anatomie*, Berlin, W. de Gruyter & Company, 1922, vol. 2, p. 410.

21. Meltzer: Mongolismus, *Klin. Wchnschr.* **57**:791, 1920.

22. Comby, J.: Le mongolisme, *Arch. de méd. d. enf.* **6**:746, 1903.

23. Thiemich: Sektionsbefund bei einem Falle von Mongolismus, *Monatschr. f. Kinderh.* **2**:134, 1903.

24. Chartier, M.: Mongolisme avec malformation cardiaque rare, *Arch. de méd. d. enf.* **9**:99, 1906.

25. Tilloy, G.: Contribution à l'étude du mongolisme, *Bull. et mém. Soc. anat. de Paris* **81**:473, 1906.

26. Cozzolino, O.: L'encefalo in un caso d'idozia mongoloide, *Pediatria* **29**:49, 1921.

27. Sutherland, G. A.: Mongolian Imbecility in Infants, *Practitioner* **63**:632, 1899; Mongolian Imbecility in Infants, *Lancet* **1**:23, 1900; Imbecility of the Mongolian Type, *Proc. Roy. Soc. Med.* **2**:187, 1909.

Lange was the first to report pathologic changes in the adrenal glands—necrotic changes consisting in atrophy of the cell bodies and granular degeneration of the protoplasm. In Gordon's 2 cases there was pluriglandular involvement. In the first of his cases (age 14 months) there were cirrhosis and dysfunction of the thyroid, physiologic involution of the adrenal cortex with hypoplasia of the chromaffin substance and a normal pineal body except for the presence of a glia-lined cyst. In his second case (age 6 weeks) the thyroid and adrenal glands showed pathologic changes identical with those in the first case; furthermore, retrogressive changes, i. e., Hassall's bodies in increased numbers, hypoplasia of the cortex of the thymus and incipient atrophy of the anterior lobe of the pituitary body, were noted.

In spite of the paucity of pathologic changes, the possible endocrine origin of mongolism was considered by various authors. The fact that children with mongolism are the offspring of older mothers, and usually the last members of the series, when the procreative powers are at a low ebb, suggests disturbances in ovarian function, not only those based on the climacterium but those with broader pathologic implications.

The endocrinologic classification of these "ill finished" children is controversial. According to Werner,<sup>28</sup> a definite pathophysiologic factor must be instrumental in producing their distinguishing characteristics, which are so astonishingly similar, but which generally are not considered to constitute an endocrine entity. However, opinions have pointed to the endocrine glands, especially to the thyroid. Benda<sup>29</sup> is the strongest advocate of the role of endocrine pathology, maintaining that endocrine stigmas are not secondary to the defects of the central nervous system. According to him, mongolism, even if overlooked in some cases, is inevitably present at birth. The antenatal development must be independent of the endocrine glands of the embryo, as the associated malformations, such as syndactyly and septal defects of the heart, antedate the development of the endocrine glands of the embryo. Thus, the deficiency is due either to germinal inferiority or to agents within the maternal organism. Of the general characteristics of children with mongolism, Benda emphasized the features referable to the endocrine glands. The menarche is delayed; menstruation may cease entirely after a few years; there is immaturity in development of the sex organs, with absence of secondary sex characteristics. The tendency to obesity, retardation of growth, degeneration of the cartilage of the distal epiphyses and absence of premature ossification parallel the gonadal underdevelopment, dysfunction of the adrenal cortex or deficiency of the thyroid or pituitary gland, without fitting into any of

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28. Werner, A. A.: *Endocrinology*, Philadelphia, Lea & Febiger, 1937.

29. Benda, J.: *Endocrine Aspects of Monogolism*, *J. Clin. Endocrinol.* 2: 737, 1942.

the classic categories. Again, Benda stressed that if the age and sex of the patient with mongolism are considered, the apparent contradiction in the endocrine aspect disappears. The gonads of the babies with mongolism are normal; those of the adults show immaturity, with degenerative signs. Similarly, the cortex and medulla of the adrenal glands are normal after birth but fail to develop normally. The pathologic process is evident in the two outer layers; the zona fasciculata appears narrow, without the usual lipid contents. The thyroid was hypoplastic in all cases in his series, the seeming exception being 2 cases of lymphadenoid goiter and colloid goiter, respectively. Histologic examination after birth revealed large areas of microfollicular parenchyma without colloid or irregular fibrosis. After the age of 7 months the commonest general picture is that of hypoplastic colloid goiter. In contrast to the thyroid of cretinism, with its inability to produce and store colloid, the type associated with mongolism retains this ability but is inactive, owing to lack of stimulation by the thyrotropic hormone of the pituitary gland. The picture of the thyroid is that of a hypoplastic and hypofunctional gland. The pathologic changes in the gonads, according to Benda, are based on lack of gonadotropins from the pituitary gland and from those glands (adrenal cortex and thyroid) which influence the gonadal development. In a more recent work, Bixby and Benda<sup>30</sup> studied the production of androgens in persons with mongolism and established apparently normal levels, indicating the deficiency of androgens from the second source, the male gonad; this corresponds to the known pathologic facts, namely, that the male gonad tends not to reach maturity in persons with mongolism and that there is absence of spermatogenesis, due to lack of gonadotropic activity of the pituitary gland. On the other hand, in the female the urinary excretion of androgens was normal, especially considering the biologic immaturity, showing that the adrenal glands are not of primary pathognomonic significance.

Kreyenberg concluded that the disturbance of the entire system of internal secretion, including the vegetative centers, is either a primary polyglandular insufficiency or a secondary insufficiency, due to general developmental inhibition or to abnormal germ plasm. Portius<sup>31</sup> similarly reasoned that the disturbance of internal secretion, especially the great disturbance in development of the genital organs, is an important cause of mongolism. The case observed by Scheidt<sup>32</sup> is of questionable

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30. Bixby, E. M. F., and Benda, C. E.: Androgens in Mongolian Idiocy, *Am. J. Ment. Deficiency* **49**:138, 1944.

31. Portius, W.: *Mongolismus*, *Fortschr. d. Erbp. d. 2*:281, 1938.

32. Scheidt, W.: Einige Ergebnisse biologischer Familienerhebungen, *Arch. f. Rassen- u. Gesellsch.-Biol.* **17**:129, 1925.

value, since the soft, toxic goiter, epicanthus, oblique palpebral fissure and yellowish skin gave the impression of mongolism, but the characteristics were only superficially similar and the picture was not that of true mongolism. Hill, in his first case, noted evidence of sclerosis of the thyroid, domination in number and size of the vesicles, though lined with regular cuboidal epithelium and filled with well staining colloid material, and greatly increased interstitial tissue with round cell infiltration; but he expressed the belief that there is as yet no evidence that any alteration, either in structure or in function, is responsible for this form of idiocy. It is generally accepted that infantile myxedema (cretinism), in which athyreosis probably exists in utero, is sharply differentiated from mongolism, the latter being characterized by absence of manifestations of hypothyroidism and the former showing striking improvement after administration of thyroid, particularly if the treatment is instituted early. Cameron<sup>33</sup> stated that the child with mongolism does not have hypothyroidism, although Benda asserted that the thyroid is hypoplastic, suggesting a resting colloid goiter, due to lack of stimulation of the pituitary body.

*Hereditary Factors.*—The endocrine background of mongolism is unconvincing, and the possible hereditary involvement has not escaped general attention. The correlation with maternal age and with familial occurrence are important factors, and the findings in twin research give valuable information.

The role of advanced maternal age in mongolism is obvious. According to Bleyer,<sup>34</sup> in 1924 the peak maternal age in this country was 24; the age of the mothers in a series of 2,822 mongoloid children was 41. Furthermore, the likelihood of producing a child with mongolism increases in direct proportion to the number of menstrual cycles through which the woman has passed. The important correlation with advanced maternal age is demonstrated by the fact that mothers from 15 to 19 years of age produced 3.4 per cent, or only one fourth of the expectancy as judged by their proportionate contribution to the total number of births, whereas the mothers from 33 to 39 years of age, producing only 0.9 per cent of births in the general population, gave birth to 23.8 per cent of the infants with mongolism, an excess over the expectancy of 25:1. The mothers in the succeeding age groups, of 40 to 44, showed a further increase above the expectancy of 75:1. Figures in various series are likely to show the existing correlation between mongolism and maternal age; the paternal age seems to be of no consequence.

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33. Cameron, A. T.: *Recent Advances in Endocrinology*, ed. 5, Philadelphia, The Blakiston Company, 1945.

34. Bleyer, A.: *Role of Advanced Maternal Age in Causing Mongolism*, *Am. J. Dis. Child.* 55:79 (Jan.) 1938.

Considering the familial occurrence, MacKaye<sup>35</sup> reported that less than 20 records are available in which mongolism occurred in more than one member of the family, and that in 1 case the patient had 4 similarly affected sisters. However, one must bear in mind that infants with mongolism are often born to mothers of advanced age and are the last in a series of children, and that the misfortune of having given birth to a child so distressing will often induce the parents not to have any more children, thus influencing the statistics of familial incidence. On the other hand, it is generally known that normal children have been born before and after a child with mongolism. The statistical figures could be interpreted as indicating that mongolism is not linked with any hereditary anomaly of the endometrium or any other inheritable affliction of the mother.

The question of hereditary or nonhereditary lesions of the germ plasm gave impetus to the research on twins with mongolism; its occurrence in twins contradicts the theory that an intrauterine lesion in the developing child is the etiologic factor. Concordance in identical twins and discordance in fraternal twins in the great majority of cases leads to the inevitable conclusion that the timing of the lesion must be placed before the moment of fertilization of the ovum. However, one must consider von Verschuer's opinion, namely, that the concordance of identical twins may be due to an early lesion of nonhereditary character or to a genuine hereditary change in the germ plasm, explaining the concordance of identical twins and the discordance of fraternal twins.

The literature contains 14 cases of monozygotic twins, all of whom were concordant; 58 cases of dizygotic twins (part of whom were of opposite sexes), with only 1 of the twins affected, and 4 cases of dizygotic twins (Russell<sup>36</sup>; MacKaye; Gordon and Roberts,<sup>37</sup> and Jervis<sup>38</sup>), with both twins affected (no twins of opposite sexes).

The research on twins with mongolism led Bleyer<sup>39</sup> to the conclusion that there is true gametic mutation of a degressive type. According to de Vries, in progressive mutation the new species possesses characteristics not present in the parents; in regressive mutation some factors are absent, though present in the parents, and in degressive mutation the offspring is essentially defective throughout its structure, lacking the power of further propagation—a gametic alteration, as

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35. MacKaye, L.: Mongolism in Nonidentical Twins, *Am. J. Dis. Child.* **52**: 141 (July) 1936.

36. Russell, P. M. G.: Mongolism in Twins, *Lancet* **1**:802, 1933.

37. Gordon, R. G., and Roberts, F.: Paraplegia and Mongolism in Twins, *Arch. Dis. Childhood* **13**:79, 1938.

38. Jervis, G. O.: Mongolism in Twins, *Am. J. Ment. Deficiency* **47**:364, 1943.

39. Bleyer, A.: Indications That Mongolian Idiocy Is a Gametic Mutation of Degressive Type, *Am. J. Dis. Child.* **47**:342 (Feb.) 1934.

expressed in mongolism. MacKaye, noting that in the great majority of fraternal twins only 1 member was affected, rightly suggested the possibility of degressive mutation in the germ plasm, since regressive mutation would necessitate the occurrence of a rare mutation form in both ova, or possibly the fertilization of one ovum by two sperm cells in the case that both the fraternal twins had the disease, explanations considered as very unlikely by most geneticists. Jervis expressed the opinion that the possibility of mutation is not consistent with the occurrence of the disease in both of a pair of dizygotic twins; mutations being rare phenomena, the assumption that mutation took place independently in the two ova at the same time in 4 cases is highly improbable. Alteration of chromosomes (Macklin, Penrose) or, according to Waardenburg,<sup>40</sup> deficiency in chromosomes through failure to divide, chromosomal duplication or sectional deficiency, due to transposition or sectional duplication, was advanced as a germinal factor in mongolism. Chromosomal alterations are inherited dominantly or recessively, and this mode of inheritance is consistent with concordance in identical twins and with discordance in fraternal twins; it is also consistent with the possibility of concordance in a certain number of dizygotic twins. However, if in mongolism chromosomal factors operate exclusively, as Jervis asserted, the proportion of concordant and discordant dizygotic twins should be close to the proportion of sibships with 2 members affected to sibships with only 1 member affected. Although reliable data concerning this point are scanty, one may assume that no more, or probably less, than 1 per cent of the affected sibships show more than 1 member with mongolism. Furthermore, Jervis called attention to the fact that the proportion of concordant and discordant dizygotic twins is 68 per cent (seven times, or probably more), a significant discrepancy suggesting other than genetic factors. The assumption of defective ova would explain the concordance of identical twins but fails in the case of dizygotic twins; the role of defective nidation does not agree with the concordance of monozygotic twins; the incidence of discordance in monozygotic twins should be of the same order as that in dizygotic twins. Analysis of the findings in research on twins led Jervis finally to external factors as causative, thus explaining some concordance in monozygotic and in dizygotic twins but failing to explain the absence of discordance in monozygotic twins. Moreover, the numerical proportion of the groups, the complete concordance in identical twins and the extremely high percentage of discordance in fraternal twins, is inconsistent with such a hypothesis.

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40. Waardenburg, P. J.: *Das menschliche Auge und seine Erbanlagen*, Bibliot. Genet. 7:1, 1932.

The cause of mongolism is probably germinal, or is operative in the earliest embryonic period; but even the research on twins failed to give a decisive answer. The inconclusive evidence and the fact that mongolism is commoner among boys than girls led Rosanoff and Handy<sup>41</sup> to assume that, although the lesion of the ovum is essential, the spermatozoon is probably not without influence. The x-chromosome of the female-producing spermatozoon seems to have in some cases the power to protect the injured ovum against its tendency to develop into a child with mongolism. In this connection, the authors pointed to the observation that mongolism varies greatly in the severity of manifestations and generally exhibits the milder forms in girls, possibly owing to the partial protection by the additional x-chromosome of the female.

The ultimate cause of mongolism seems still to be undecided. The maternal age shows definite correlation; the aberration is established in the earliest prenatal life and probably is present in the ovum. Early environmental, perhaps ovarian, causative factors or inherent genetic entities, rather than regressive mutational changes, are the chief agents. If the disease is inherited, the dominant type of inheritance is ruled out by the seriousness of the condition, which, eliminating the reproduction of the afflicted person, would lead to spontaneous eradication of mongolism itself. Therefore, the recessive mode of inheritance remains as the only possibility, but the characteristic criteria of this type are absent in the sibship of children with mongolism.

Of the ocular symptoms, the characteristic oblique palpebral fissure, the nystagmus, the bulging eyes and the blepharitis have already been mentioned. Concerning epicanthus, it should be stressed that the phenotypically identical anomaly is apparently genotypically different, as it shows dominant inheritance in the white race and in Japanese and Chinese crossings with members of the white race, but is recessive in Eskimos and in Hottentot crossings with white persons.

To the ophthalmologist, the occurrence of conical cornea and cataract formation in the older patients with mongolism is of great interest. The changes in the lens are not present in the very young patients with the disease; therefore, they are not congenital but develop later. The characteristic opacities in the lens are of the same type but of somewhat different distribution, like that in myotonia atrophica, and constitute only facultative, not obligatory, symptoms of mongolism. The first to report bilateral cataract in association with mongolism was de Sanctis.<sup>42</sup> Kassowitz and Suhsland each mentioned a case of stellate cataract. The

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41. Rosanoff, A. J., and Handy, L. M.: Etiology of Mongolism, with Special Reference to Its Occurrence in Twins, *Am. J. Dis. Child.* **48**:764 (Oct.) 1934.

42. de Sanctis, G. E.: Osservazione sulla etiologica del cheratocono, *Ann. di ottal. e clin. ocul.* **65**:279, 1937.



first study of a large series, 19 of 28 cases of mongolism, was made by Pearce, Rankine and Ormond,<sup>43</sup> and the same cases were considered later, with good illustrations, by Leeper.<sup>7</sup> Cassel<sup>44</sup> mentioned 3 cases of cataract in 60 cases, and Geyer, 4 cases in 30 cases of mongolian imbecility; and the occurrence of such cataracts was confirmed by von der Scheer,<sup>45</sup> Jeremy, Koby, Weill and Nordman, Goulden, Pineles, Vontobel, Schroeder, Doxiades and Portius. Of the 60 patients who were reported on by von der Scheer, 10 were under the age of 10 years, with completely clear lenses; 14 were 17 years or older and all exhibited bilateral cataract, and the group between the two, comprising patients between the ages of 8 and 17 years, consisted of 32 persons, with 22 afflicted with cataract. The lenticular changes were not congenital and were characterized by slow progression, unlike that of tetany, which is always rapid. With age, the frequency and the intensity of cataractous changes show parallel increases. Pearce, Rankine and Ormond, similarly, could not detect lenticular opacities in children under the age of 9 years; the fully developed cataract was present only in the older patients, and the less mature form, in some of the other patients. The distribution of the opacities, according to Duke-Elder,<sup>46</sup> resembles closely that seen in cases of myotonia, although the arrangement of the opacities points to an earlier development.

The minute dots may be powdery or punctate; others are annular or flaky; some are of crystalline appearance. The majority are white, while others glitter with red or green light. The dots are located in the cortical portion, deep to the capsule, and are nearer the anterior than the posterior surface. They are best seen with focal illumination, the small size causing them to be invisible in transillumination. In the cases of mature cataract the opacities consist of two layers enclosing the clear fetal nucleus, the posterior lamella having its anterior face concave and corresponding in curve to the posterior surface of the lens. The anterior lamella is much flatter and is situated about midway between the center of the nucleus and the surface of the lens. The dots are more numerous axially than peripherally and never reach the equator. The posterior pole of the cataract coincides with the posterior pole of the lens and may be arranged in a stellar figure. The anterior pole of the cataract does not correspond with the anterior pole

43. Pearce, F.; Rankine, R., and Ormond, A.: Notes on Twenty-Eight Cases of Mongolian Imbeciles, *Brit. M. J.* 2:187, 1910.

44. Cassel: Ueber Missbildungen am Herzen und an den Augen bei Mongolismus der Kinder, *Berl. klin. Wchnschr.* 44:159, 1917.

45. von der Scheer, W.: Cataracta lentis bei mongoloider Idiotie, *Klin. Monatsbl. f. Augenh.* 62:155, 1919.

46. Duke-Elder, S. W.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

of the lens. Leeper mentioned that the fully developed form may be described as lamellar cataract and the slighter form as congenital punctate cataract. The descriptions of later observers agree with that outlined here; some investigators, such as Vontobel, designated it as *cataracta cerulea* of the deeper cortical layers, and von der Scheer noted perinuclear cataract in 2 of his 80 cases. Fleischer attributed the formation of cataract in cases of myotonia to disturbance of the glands of internal secretion, and Duke-Elder pointed to the hypofunction of the thyroid in cases of mongolism as a possible basis of the lenticular opacities.

The inner eye shows the lenticular changes in large proportion of the older patients with mongolism, but, less frequently, central and para-central degenerative patches of the retina and macular degeneration were also noted in the older group. An exception is the case of Boros,<sup>47</sup> in which a 5 month old infant with mongolism had a small, pigment-framed hole in the right macula and a large, disk-sized, oval, pigment-framed, sharply punched-out hole in the left macula. In this case the hole formation was due to intrauterine degeneration, as indicated by the ring of pigment surrounding the hole; nevertheless, the absence of retinal development could not be excluded.

## CONICAL CORNEA

### ASSOCIATION WITH VERNAL CONJUNCTIVITIS

In the introductory section, the occurrence of conical cornea with mongolism was mentioned, the only generalized systemic disease known to be associated with the development of this corneal lesion. Of the local diseases of the eye, vernal conjunctivitis is known to be associated with conical cornea, as first described by Lodato, in 1910, and confirmed by Tristiano, Rizzo, Gennaro,<sup>48</sup> Padovani,<sup>49</sup> Bietti<sup>50</sup> and Satanowsky.<sup>51</sup> The relation of vernal conjunctivitis and keratoconus was based on the opinion expressed by the authors that the endocrine disturbance was responsible for the two conditions; Parovani's patient, a man aged 22, had vagotonía (dermographia, the oculocardiac reflex and a strong reaction to vagotropic substances) and showed a feminine distribution of

47. Boros, B.: *Beiderseitige Lochbildung in der Macula lutea bei mongoloider Idiotie*, *Klin. Monatsbl. f. Augenh.* **103**:91, 1939.

48. Gennaro, G.: *Sui singolari rapporti tra il cheratocono e il catarro primaverile della conjunctiva*, *Gior. med. mil.* **76**:464, 1928.

49. Padovani, S.: *Aritmia endocrina in soggetto primaverile con cheratocono*, *Lettura oftal.* **2**:442, 1934; abstracted, *Zentralbl. f. d. ges. Ophth.* **33**:213, 1935.

50. Bietti, G.: *Sui risultati del metodo interferometrico nel campo endocrinologico oculare*, *Boll. d'ocul.* **17**:370, 1938.

51. Satanowsky, P.: *Vernalis and Conical Cornea*, *Acta Cong. argent. oftal.* **2**:193, 1938.

hair and fat and acrocyanosis. Bietti, by using the interferometric method of Hirsch, concluded that dysfunction of the genital organs was the plausible explanation in his 2 cases.

#### ENDOCRINE AND HEREDITARY FACTORS

In the vast majority of cases of conical cornea the lesion occurs in apparently healthy persons; disregarding the cases associated with mongolism and vernal conjunctivitis, one may consider the etiologic theories as of two types: The first type endeavored to explain conical cornea as a partial symptom of disturbance of the glands of internal secretion; the second looked to inheritance to furnish the unknown cause of the development.

The possible involvement of the endocrine system in cases of conical cornea became a much discussed problem after Siegrist<sup>52</sup> pointed to hypothyroidism as an important factor. Endocrine imbalance may influence the cornea, a primarily supportive tissue, a claim borne out by the bilateral appearance of conical cornea, often at about the age of puberty. Thus, conical cornea was regarded as an environmental anomaly in the older literature, at a time when blood pictures due to such conditions as chlorosis, anemia, undernourishment and underweight were unknown. Dor reported a case of bilateral conical cornea with exophthalmic goiter in which organotherapy effected improvement in both conditions; however, it is hard to believe that any treatment would result in *restitutio ad integrum*, the complete disappearance of clinical changes, once established, and the reappearance of a normal cornea in man. The results of animal experimentation cannot be applied directly to the explanation of conical cornea in human beings; it is more than questionable whether the condition produced in animals is identical in development. The experimental results of Mutch and Richards,<sup>53</sup> postulating that conical cornea is a vitamin A deficiency disease, must be regarded cautiously. Gudjonsson was the first to mention that in his experiments, in which keratomalacia was produced by a vitamin A-free diet, conical cornea developed frequently; but Mutch and Richards stated that the illustrations presented not keratoconus but buphthalmos. The latter authors administered a vitamin A-free diet to rats after weaning until the appearance of clinical symptoms of the deficiency were noted, and subsequent administration of large doses of vitamin A produced an acute form of conical cornea; if the vitamin was given early, the eyes cleared up completely and rapidly. The conical cornea was

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52. Siegrist, A.: Die Behandlung des Keratoconus, Klin. Monatsbl. f. Augenh. 56:400, 1916; Zur Aetiologie des Keratokonus, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. 38:187, 1912.

53. Mutch, J. R., and Richards, M.B.: Keratoconus Experimentally Produced by Vitamin A Deficiency, Brit. J. Ophth. 23:381, 1939.

reversible in their experiments, and the cornea regained its normal contours, with only nebulas persisting. In the majority of their cases anterior synechias were noted; the pupils either failed to dilate or dilated only irregularly, changes which led the authors to suggest that increased intraocular pressure may have been the causative factor. Interesting as these experiments are from the standpoint of vitamin A deficiency, one must note, first, that the picture was reversible and complicated by intraocular changes; second, that, as shown in the illustration, the process not only involved the central portions but extended in all directions to the periphery, features hardly like those of conical cornea in man.

Siegrist noted that conical cornea occurs in delicate, nervous, pale persons, with dry skin, decreased perspiration, loss of hair and poor memory; and examination of the blood by Siegrist and Kottman revealed increase of lymphocytes and accelerated coagulation time, suggesting hypothyroidism. Strebel and Steiger<sup>54</sup> established that patients with known hypothyroidism, e. g., myxedema, do not have conical cornea, and they could not confirm the findings of Siegrist and Kottman. Of 9 patients with hypothyroidism, 6 did not show these changes; 3 had a slight increase of lymphocytes, and all 9 had normal coagulation time; the clinical symptoms were either absent or present to such a minimal degree as that encountered in normal persons without involvement of the thyroid gland. Siegrist countered with criticism of Strebel and Steiger's case histories, asserting lack of clarity and claiming that a patient may exhibit typical features in the beginning or during the period of progression, but that the absence of these signs after the condition has persisted for twelve to sixteen years is not conclusive. Furthermore, the reliability of the lymphocyte count was questioned by Siegrist, since Strebel and Steiger did not make the tests when the stomach was empty, and the digestive leukocytosis might interfere with the picture of an increased lymphocyte count. Siegrist observed conical cornea in 2 persons each 17 years of age, 1 with endemic cretinism and atrophy of the thyroid gland and the other a mongolian idiot. The case of Scheidt (not one of mongolism) and Wibo's case of conical cornea accompanying myxedema are further examples of conical cornea with an established pathologic condition of the thyroid. Nevertheless, these observations are meager as compared with the extensive distribution of thyroid disturbances in the population in general.

Von Hippel,<sup>55</sup> following the reasoning of Siegrist, expressed dissatisfaction with the view of the significance of the clinical symptoms

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54. Strebel, J., and Steiger, O.: Ueber Keratokonus: Seine Beziehungen zur inneren Sekretion und zum intraokularen Druck, *Klin. Monatsbl. f. Augenh.* **15**: 260, 1913.

55. von Hippel, E.: Zur Aetiologie der Keratokonus (Untersuchungen mit der Abderhaldenschen Dialysierverfahren), *Klin. Monatsbl. f. Augenh.* **16**: 273, 1913.

of endocrine disturbance in cases of conical cornea, since they are inconstant and do not permit any conclusion as to which gland is at fault. To bring further clarity to the problem, he employed the method, at that time considered more dependable, the dialyzation test of Abderhalden. In 2 typical cases and in 1 closely related case, the serum reacted to thymus—in 1 exclusively and in the others more strongly than to any other gland employed. Next to the thymus, a strong reaction was obtained to the adrenal gland in 2 cases; the reaction to thyroid was negative in 1 case and slightly positive in 2 other cases. In 1 case there was a slight reaction to pancreas; in another, a questionable reaction to the pituitary gland. In a later series of cases,<sup>56</sup> the reaction in 1 case was positive to thymus and testis and only slightly positive to thyroid; in a second case, slightly positive to thymus and thyroid; in a third case, slightly positive to thyroid, thymus and pancreas, and in a fourth case, positive to thymus, thyroid and spleen. On the basis of these results, he concluded that a relation between conical cornea and disturbance of the endocrine glands probably exists, but he warned of difficulty in interpretation, as the behavior of serums differs with time, a formerly positive reaction becoming negative and thus complicating the question, especially in cases of long standing. Hack<sup>57</sup> applied the same method in 3 of his cases; in the first case, a positive reaction was registered to brain and exophthalmic goiter tissue (negative in a subsequent examination five weeks later); in the second case, one of keratectasia following syphilitic keratitis, the reactions were negative, and in the third case the reaction was positive only to thymus. Dodge,<sup>58</sup> in 4 of 5 cases, observed an increased urinary excretion of sugar in the glucose tolerance test; this increase, due to a low normal threshold, suggests a lesion of the pituitary gland or the floor of the third ventricle. In a second series, of 34 cases, von Hippel<sup>59</sup> reported negative reactions in 6 cases, multiple reactions in 20 cases, with a reaction to thyroid only in 1 case and to thymus only in 7 cases, the total number of positive reactions to thyroid being 17 and to thymus 25. The series proved the occurrence of multiple reactions to various glands. These results were misunderstood by Kraupa,<sup>60</sup> who interpreted them as inconsistent, thinking that Siegrist suggested hypothyroidism as a

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56. von Hippel, E.: Ueber die Behandlung des Keratokonus mit den Muellerschen Kontaktgläsern, *Klin. Monatsbl. f. Augenh.* **60**:49, 1918.

57. Hack, J.: Zur Aetiologie des Keratokonus, *Arch. f. Augenh.* **76**:259, 1915.

58. Dodge, W. M.: Keratoconus: Report of Five Cases, *Am. J. Ophth.* **21**:40, 1938.

59. von Hippel, E.: Untersuchungen über Keratokonus mit dem Abderhaldenschen Dialysierverfahren, *Arch. f. Ophth.* **90**:173, 1915.

60. Kraupa: Physiognomisches bei Keratokonuskranken, *Ber. d. deutsch. ophth. Gesellsch.* **43**:294, 1922.

factor in the causation of acquired conical cornea, followed by dysfunction of the thymus and ovaries, and questioned why, for example, the parathyroid glands and the pancreas, glands which clinically are known not to result in the formation of conical cornea, were not similarly mentioned. Kraupa's argument was fallacious; a pluriglandular involvement remains an unproved possibility, as von Hippel's results can be interpreted only as a pluriglandular reaction, with predominance of the thyroid and thymus. The results of Schnaudigel<sup>61</sup> are further proof in support of this hypothesis. Of 9 cases, a positive reaction to thymus was registered in all, to thyroid in 5 and to the pituitary gland in 4 (only 6 cases were studied). Lymphocytosis was noted only in 2 cases, of the severe form. According to Schnaudigel, the positive reaction to thymus occurs so often in cases of toxic goiter and status thymicolymphaticus that its significance must be denied.

The endocrine involvement has often been questioned on account of undoubted unilateral disturbances; but this argument is not convincing, as proved by the occurrence of unilateral exophthalmos in cases of toxic goiter. The frequent development of conical cornea with the menarche, its relatively infrequent appearance at the menopause and the progressive course during the latter in cases of long standing (Killick) are suggestive of gonadal disturbance, possibly due to dysfunction of the pituitary gland. In 1 of Siegrist's cases, von Hippel found a positive reaction to ovary, and gynecologic examination disclosed infantilism; a similar case was observed by von Hippel, in which a 19 year old girl appeared to be only 14. Imre reported 4 cases with dysfunction or hypofunction of the ovaries; Padovani, a case of acrocyanosis and feminine distribution of the pubic hair and fat, and Meerhoff, Meerhoff and Montes Pareja,<sup>62</sup> the case of a 14 year old boy with genital hypoplasia and symptoms of dystrophia adiposogenitalis without any change in the sella turcica. In Gennaro's cases of 2 brothers, aged 19 and 26, respectively, the genitalia were poorly developed, and Jaensch's<sup>63</sup> patient, a boy aged 14 years, had dystrophia adiposogenitalis.

Dysthyroidism may serve as explanation of conical cornea in the case of Augstein,<sup>64</sup> in which toxic goiter was accompanied with dry,

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61. Schnaudigel, O.: Zur Therapie des Keratokonus, *Klin. Monatsbl. f. Augenh.* **69**:466, 1922.

62. Meerhoff, W.; Meerhoff, A., and Montes Pareja, J.: *Arch. de oftal. de Buenos Aires* **4**:129, 1929.

63. Jaensch, P. A.: Keratokonus, *Med. Klin.* **25**:862, 1929; Keratokonus, die Ergebnisse der Forschungen der letzten 20 Jahre, *Zentralbl. f. d. ges. Ophth.* **21**: 305, 1929.

64. Augstein, C.: Zur Aetiologie und Therapie des Keratokonus, *Klin. Monatsbl. f. Augenh.* **51**:417, 1913.

pale skin, dystrophia of the nails and lymphocytosis, but no change in the coagulation time. Similarly, Verderame<sup>65</sup> observed parenchymatous enlargement of the thyroid, especially on the side of the large conical cornea. Sitchevska reported hypothyroidism in 6 cases; the trophic disturbance manifested itself in falling of the hair, brittleness of the nails, dryness of the skin (4 cases), hypertrichosis (1 case), increase of lymphocytes (3 cases), acceleration of coagulation time (4 cases) and a normal basal metabolic rate in all cases. The Abderhalden test disclosed hypofunction of the thyroid and thymus in 1 case; the blood calcium in all cases was within normal limits, and no rarefaction of the cranial bones was noted. Of Natale's 3 cases, negative reactions to thyroid were established in 2 cases, and positive reactions to thymus (with ovary, testis and pituitary), in 3 cases. Amoretti noted more positive reactions to thyroid than to thymus; Hack had a positive reaction to thymus in 1 of 3 cases. Suzuki,<sup>66</sup> with the interferometric method, reported dysfunction of the thyroid and pituitary gland in 1 case. In 3 of de Sanctis' 5 cases (1 of mongolism), the sella turcica was enlarged sagittally without clinical signs of endocrine imbalance, but possibly abnormalities of the pituitary gland were responsible for the enlargement of the sella. Velhagen<sup>67</sup> described an acute form of conical cornea with trophic disturbances and with questionable involvement of the thyroid and parathyroid glands. Dysthyroidism was claimed as the etiologic factor in 2 cases by Tamasheff<sup>68</sup>; tachycardia was present in both cases, and lymphocytosis and accelerated coagulation time were noted in 1. In 1 of Fleischer's<sup>69</sup> cases the Abderhalden reaction to thymus was positive, but it is noteworthy that, in Kraupa's opinion, the case represented keratectasia rather than conical cornea. In 11 cases reported by Fleischer and associates,<sup>70</sup> neither lymphocytosis nor acceleration of the coagulation time was evident; anomalies of the thyroid were associated with only 2 of his cases, in the form of slight enlargement but without anomalies of the hair, nails or skin. Groth, Hack and Uhthoff,<sup>71</sup> similarly, denied the endocrine basis of

65. Verderame, F.: Weitere Beiträge zum Verhalten der Pupille beim Keratokonus, *Klin. Monatsbl. f. Augenh.* **78**:145, 1927.

66. Suzuki, S.: *Acta Soc. ophth. jap.* **35**:1336, 1931.

67. Velhagen, K.: Einzelbeobachtungen über Störungen der inneren Sekretion und Auge, *Klin. Monatsbl. f. Augenh.* **96**:577, 1936.

68. Tamasheff, I. I.: The Etiology of Keratokonus, *Russk. vrach* **13**:127, 1914.

69. Fleischer, B.: Beitrag zur Klinik des Keratokonus, *Arch. f. Augenh.* **74**:110, 1913.

70. Fleischer, B.; Schloessman, and Broesamlen: Beitrag zur Klinik des Keratokonus, *Arch. f. Augenh.* **74**:110, 1913.

71. Uhthoff, W.: Weitere klinische und anatomische Beiträge zum Keratokonus, *Klin. Monatsbl. f. Augenh.* **56**:385, 1916.

conical cornea; Uhthoff found slight tachycardia with leukocytosis in 1 instance and slight toxic goiter with tachycardia in 2 others; in his opinion, the presence of minimal general disturbances does not warrant the assumption of any link between the endocrine status and conical cornea.

Imre <sup>72</sup> and von Szily <sup>73</sup> independently cited Török and Redway's <sup>74</sup> 3 cases, in which there were a decreased basal metabolic rate, anemia, signs of disturbance of calcium metabolism and changes in the cranial bones, but both fortuitously omitted to mention Török's second paper, <sup>75</sup> contradicting his own previous findings. The researches of Blackberg and Knapp <sup>76</sup> belong in the same category. They reported consistent production of conical cornea in dogs and rats fed a diet deficient in vitamin D and low in calcium, pointing out the importance of calcium-phosphorus metabolism in the development of the cornea.

An entirely different approach to the problem of conical cornea was presented by Vázquez and Barrière. They observed a greater than normal prominence of corneal nerve filaments and diminution of corneal sensibility in cases of venereal lymphogranuloma and obtained a positive reaction to the Frei test in all of a series of 14 cases of conical cornea. May confirmed the results by obtaining a positive reaction in all but 1 of his 29 cases. Nevertheless, Rocha <sup>77</sup> arrived at contradictory results. Of 20 patients, only 3 had a positive reaction to 0.1 cc. of the Frei antigen, and 6 who reacted negatively were retested with 0.3 cc., with a positive reaction in only 1 case. On the other hand, examination for an endocrine factor in 10 cases revealed hypothyroidism in 7 cases, hyperthyroidism in 2 cases and hypogonadism in 1 case.

Von Hippel maintained that Siegrist's opinion concerning hypothyroidism as an etiologic factor was well founded but called attention to the involvement of the thymus, as shown by serologic tests. The symptoms of disturbance of the thymus are much harder to detect than the distinct clinical symptoms of imbalance of other glands, such as the

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72. Imre, J.: Eye Diseases and Symptoms Connected with the Gonads, Adrenals, and Pregnancy, *Tr. Internat. Ophth. Cong.* (1937) **3**:181, 1938.

73. von Szily, A.; Schilddrüse und Auge, *Tr. Internat. Ophth. Cong.* (1937) **3**:103, 1938.

74. Török, E., and Redway, L. D.: A Preliminary Report of Three Cases of Keratokonus, *Arch. Ophth.* **57**:19, 1928.

75. Török, E.: Three Cases of Keratoconus: Final Report, *Arch. Ophth.* **4**: 348 (Sept.) 1930.

76. Blackberg, S. N., and Knapp, A. A.: Ocular Changes Accompanying Disturbances of Calcium-Phosphorus Metabolism, *Arch. Ophth.* **11**:665 (April) 1934. Knapp, A. A.: Vitamin D Complex in Keratoconus: Etiology, Pathology and Treatment of Conical Cornea, *J. A. M. A.* **110**:1993 (June) 1938; Results of Vitamin D Complex Treatment of Keratoconus, *Am. J. Ophth.* **32**:289, 1939.

77. Rocha, A.: Keratoconus, *Rev. brasil. oftal.* **3**:123, 1945.



thyroid or the gonads. Various observers have advanced the hypothesis that one of several glands or a polyglandular involvement is the causative factor. Duke-Elder mentioned a possible endocrine involvement but, at the same time, emphasized the hereditary aspect of the problem.

The familial occurrence of conical cornea, or horizontal inheritance, was noted as early as 1828 by von Ammon in 3 members of the same family, and Horner described the vertical inheritance of the defect in two generations. Since these observations, there have been numerous references in the literature to the familial and hereditary occurrence of keratoconus. Various authors have observed the anomaly within the same sibship: Stähli<sup>78</sup> described it in 2 sisters; Wölfflin, in 2 sisters (according to the history, the father and mother were also affected [Wolz's<sup>79</sup> third case]); Killik, in 2 families; Haab, in 2 brothers (the lesion was more pronounced on the right side); Borel, in 2 brothers (Wolz's second and fourth cases); Gennaro, in 2 brothers; van der Hoeve,<sup>80</sup> in a brother and sister, and in a brother and 2 sisters; Weill,<sup>81</sup> in a brother and sister in 2 families; Dor, in several members of the same family (always on the left side); Kaelin-Sulzer,<sup>82</sup> in 2 brothers in a family of 8 children (consanguinity was not proved, but it could not be entirely excluded, for the parents had the same family name and so the relation of the mother's parents may have gone back farther than could be ascertained); Rumpf,<sup>83</sup> in 2 sisters (with brittleness of the nails), in a sister and 2 brothers and in a brother and sister (consanguinity was not present); Abelsdorff,<sup>84</sup> in 2 sisters, and Sander,<sup>85</sup> in 3 sisters, whose father had keratoconus. All the 4 affected persons in Sander's observation had various degrees of long-standing and neglected trachoma with sequelae, vascularization and scars of the cornea and entropion; all 4 members had anterior polar cataract with the conical cornea (similar to the observation of de Lapersonne).

Cases showing vertical inheritance are those of Clausen (mother and daughter), Haab, Wachter, Weill and Coppez (father and son) and the

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78. Stähli, J.: Weitere Mitteilungen über die Vererbung des Keratokonus, *Klin. Monatsbl. f. Augenh.* **75**:465, 1925.

79. Wolz, O.: Zur Frage der Vererbbarkeit des Keratokonus, *Arch. f. Augenh.* **92**:156, 1923.

80. van der Hoeve, J.: Vererbbarkeit des Keratokonus, *Ztschr. f. Augenh.* **52**:321, 1924; **53**:342, 1924.

81. Weill, G.: Sur l'étiologie de kératocône, *Ann. ocul.* **164**:668, 1927.

82. Kaelin-Sulzer, M.: Zwei Brüder mit Keratokonus, *Klin. Monatsbl. f. Augenh.* **103**:513, 1939.

83. Rumpf, J.: Contribution à l'étude de l'hérédité du kératocône, *Inaug. Dissert., Lausanne*, 1937.

84. Abelsdorff, G.: Ein Beitrag zur Erbllichkeit des Keratokonus, *Arch. f. Augenh.* **103**:293, 1930.

85. Sander, P.: A Family Affected with Keratokonus and Anterior Polar Cataract, *Brit. J. Ophth.* **15**:23, 1931.

previously mentioned case of Sander (father and 3 daughters). All these cases were instances of hereditary transmission within two generations, but transmission through three generations was described by de Lapersonne and Stähli. In the family observed by de Lapersonne, conical cornea and congenital cataract occurred either singly or in associated form. Stähli found 5 affected members among 9 persons comprising three generations. A normal female and an afflicted male member constituted the first generation. The only son of the affected male was similarly affected; the unaffected female had 5 children (4 girls and 1 boy), the second and fourth daughters being affected. The third daughter of the sibship, herself unaffected, had an affected daughter. There was no consanguinity. In two generations the unaffected females, and in one generation the affected male, were the transmitters. The pedigree in Abelsdorff's case shows 2 brothers in the first generation, 1 of whom was affected and 1 unaffected; the former had 7 daughters and 7 sons, and 2 daughters were afflicted in the second generation, the transmitter himself being unaffected.

Conical cornea affected cousins in the cases of Borel and von Mandach (Wolz's fifth and sixth cases), Abelsdorff (the mothers and fathers were brothers and sisters) and Vogt<sup>86</sup> (the older patient was the niece of the father of the younger one).

Hereditary transmission has been claimed in certain cases of conical cornea by various authors; but opinions as to the mode of inheritance is not unanimous, and therefore the type of hereditary involvement is uncertain. The congenital forms were occasionally associated with intrauterine or early developmental anomalies, such as blue sclera (Behr), microcornea, persistent pupillary membrane, anterior polar cataract (de Lapersonne, Sander), pigmentary degeneration of the retina, medullated nerve fibers, atrophy of the optic nerve and inflammatory changes in the optic nerve and sheath (Salzmann). According to Franceschetti,<sup>87</sup> the uncomplicated form of hereditary conical cornea often seems to follow the recessive mode of inheritance, being often observed in the same sibship and coupled with consanguinity in some instances; on the other hand, its appearance in successive generations would testify against the recessiveness; possibly, therefore, its mode of inheritance is either dominant or irregularly dominant. Ida Mann expressed the belief that the inheritance is recessive or irregularly dominant and called attention to the unilateral appearance in all members of the same family. With regard to the latter statement, one must

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86. Vogt, A.: Neue histologische Befunde bei Cornea guttata, *Ztschr. f. Augenh.* 84:21, 1934.

87. Franceschetti, A.: Vererbung von Augenleiden, in Schieck, F., and Brückner, A.: *Kurzes Handbuch der Ophthalmologie*, Berlin, Julius Springer, 1931, vol. 1, p. 732.

recall that the expression of a hereditary factor may differ greatly, as shown by polydactyly, which is a typical instance of simple dominant inheritance. The bilateral expression may be greatly modified as a result of variations in expression of the gene, due to differences in respect to other genes or differences in environmental conditions or both, or to the presence of inhibiting or modifying genes, producing only unilateral expression of the gene. However, in cases of conical cornea one would have to observe the family for a long time, for the manifestly normal eye may develop conical cornea after an interval of many years, or the conical cornea of the other eye may be represented by *forme frustre*, with a high degree of astigmatism, without the clinical picture of keratoconus. The occurrence of hereditary unilateral conical cornea seems not to be outside the realm of possibility; but the available data are insufficient for a conclusion, and it remains for future research to establish its occurrence with certainty. Schieck<sup>88</sup> accepted the hypothesis of the hereditary disposition of the condition but pointed out that, nevertheless, cases of congenital conical cornea had not been observed. This apparent contradiction is refuted by knowledge that conical cornea belongs in the group of conditions of homochronous inheritance, with the usual manifestation about the age of puberty. Waardenburg gave the mode of inheritance as recessive or dominant. However, the pedigree in van der Hoeve's case is typical of recessive transmission, as proved by the numerical ratio of the homozygotes and heterozygotes. Similarly, Clausen claimed transmission as a recessive, but suggested the possibility that conical cornea is not a simple factor and that its heredity may therefore be complex.

#### CONICAL CORNEA AND MONGOLISM

The available data on mongolism and conical cornea are sufficient to be conclusive. The association of the two conditions was at first only occasionally mentioned by de Sanctis and Siegrist, but the accumulation of cases demonstrate that the occurrence is not due alone to chance but belongs, like the cataract of older persons with mongolism, to the facultative characteristics of mongolian imbecility. The occurrence must, of necessity, be infrequent; conical cornea is rare in young persons (Gilbert noted it in 2 patients, 7 and 8 years of age, respectively). In Jaensch's compilation of 56 cases (20 male and 36 female patients) the congenital type occurred in 2 cases; the lesion developed between the ages of 10 and 14 in 8 cases, between the ages of 15 and 24 in 31 cases, between the ages of 25 and 29 in 7 cases, between the ages of 30 and 39 in 1 case and after the age of 40 in 1 case. In the majority

88. Schieck, F., in Schieck, F., and Brückner, A.: *Kurzes Handbuch der Ophthalmologie*, Berlin, Julius Springer, 1931, vol. 4.

of cases conical cornea develops at about the age of puberty or shortly after; on the other hand, the majority of children with mongolism do not reach the age of puberty, these two facts explaining the relative infrequency of the combination.

The mechanism of the establishment of conical cornea must be based on differences in degrees of consistency either of the entire cornea or of the central portion, whether the concept of a developmental anomaly or a disturbance of growth is accepted. The decrease in consistency due to structural deficiency of the tissues, mainly of the elastic elements, was suggested by Parisotti; decrease in the elastic coefficient, suggested by Parinaud and Pollak, and congenital weakness of the corneal center (or degeneration of Descemet's membrane), proposed by Ellis,<sup>89</sup> were unsatisfactory in themselves to explain even the congenital cases, and therefore additional local factors, such as increased intraocular pressure or inflammatory changes in Descemet's membrane or the endothelial layer, were sought, but were proved not to be operative. Additional causes of the mechanism were sought, such as an acquired decrease in resistance due to disturbances in the glands of internal secretion—mesenchymal weakness due to deficiency of the pituitary gland, or hypofunction of the gonads, thyroid or thymus—avitaminosis or calcium deficiency. The question of decreased resistance as a factor in conical cornea remains unanswered; Stähli<sup>90</sup> turned to the biologic law of variability in keratoconus. The curvature and measurement of the cornea are elements in the variability; Stähli assumed that this variability is operative in determining the thickness of the cornea, resulting in the two extremes, the very thick and the very thin type, the latter being necessarily of decreased resistance; the same variability must govern the elasticity and resistance coefficients. This variability, in accordance with biologic laws, can be postulated only, for there are no means of clinical measurement, and histologic examinations are entirely unreliable, owing to the presence of various late changes.

The question of variability leads to the hereditary involvement of the germ plasm, for hereditary weakness need not manifest itself at birth, but weakness may be inherent as a homochronous form of hereditary transmission, and come to expression without any auxiliary moment (as in hereditary degeneration of the macula), or, probably, by inducing such moments as endocrine dysfunction, with mesenchymal weakness. With regard to the latter, it is worthy of mention that in 1 of the cases

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89. Ellis, J. W.: Keratoconus with Demonstration of Cases, *Texas State J. Med.* 20:327, 1924.

90. Stähli, J.: Das Krankheitsbild des Keratokonus vom Standpunkte der Variabilitätslehre mit zwei klinischen Beispielen vom Familiarität des Keratokonus und einem Anhang mit Bemerkungen zur Myopiefrage, *Klin. Monatsbl. f. Augenh.* 62:712, 1919.

in the pedigree of van der Hoeve, with unquestionable recessive hereditary involvement, the Abderhalden test gave a positive reaction to thyroid. The clinical observation of progressiveness of a preexisting conical cornea during pregnancy may serve as another illustration.

The possibility remains that conical cornea is a clinical entity, either hereditary or acquired, without hereditary characteristics, based on pathologic changes in the endocrine gland. The association of conical cornea with mongolism raises important problems. In both conditions an endocrine disturbance, possibly polyglandular, may be operative, either primary or as a result of a general developmental abnormality in the germ plasm. The occurrence of conical cornea in cases of mongolism permits the conclusion that the nonhereditary form of keratoconus must be associated with endocrine imbalance characteristic of mongolism and, furthermore, that in the complex transmission of the anomaly the genetic factors may influence the cornea directly or through a possible inherited dysfunction of the endocrine glands.

31 Lincoln Park.

## Book Reviews

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**Children's Eye Nursing.** By James Hamilton Doggart, M.A., M.D., F.R.C.S. Price, 9s. 6d. Pp. 144, with 93 illustrations, 13 in color. London: Henry Kimpton, 1948.

The pediatric nurse has certain problems and consequent technics differing somewhat from those of her sister in general nursing. There are also a few disparities between the work of a nurse who takes care of children's eyes and that of her colleague who performs a like function for adults. To meet this situation, Doggart has written a little volume which he thinks "can be of some help." There are chapters on anatomy, etiology, inflammations, squint, injuries, instruments and dressings; but it must be admitted that the book overflows the limits inherent in its title. The format is convenient, and the illustrations are clear.

G. M. BRUCE, M.D.

**Transactions of the Ophthalmological Society of Australia (British Medical Association).** Volume 7. Price, 15s. Pp. 143, with 17 illustrations. Sydney, Australia: Australasian Medical Publishing Company, Ltd., 1947.

This volume comprises the transactions of the 1947 meeting of the Australian Ophthalmological Society. The president's address, delivered by D. A. Williams, was a résumé of the history of ophthalmology in Australasia. N. M. Macindoe reported on the results of a visit that he made to Europe and the United States. He discussed the work that he observed on permeability of the cornea, retrobulbar neuritis and visual acuity at Harvard; virus diseases and corneal grafting, at Johns Hopkins; color vision and lighting standards, at the Institute of Ophthalmology in New York; biochemistry of the ocular media, in Basel; corneal distortions, subjective screens, content of the aqueous, permeability of the ciliary body and tonometry, at Zurich; perimetry, at Berne; strabismus, at London; electroretinography and monochromatic light, at Stockholm, and colloidometry, at Copenhagen. He states that Australia is lagging seriously behind other countries in the training of qualified ophthalmic surgeons.

J. B. Hamilton, who has been continuing his work on dry eyes, reported 24 additional cases. In his paper on "Protection of the Eyes in Industry," A. L. Tostevin classified industrial accidents on the basis of cause and of the agent responsible. W. L. Gibson has had a radon seed made in the form of a circle, so that it can easily be sutured to the globe in cases of retinoblastoma. He stated the belief that the maximum surface dose is 7,000 r and the average tumor dose 4,000 r. Two cases of intraocular tumor, a melanoma of the choroid of four years' duration and a retinoblastoma with extension, were reported by Kevin O'Day. The article is accompanied with excellent photomicrographs.

J. A. O'Brien, reporting on 60 cases in which the Lagrange operation was performed, stated that in his opinion this procedure presents

fewer complications and offers a higher percentage of successes than any other. A case of endothelial dystrophy was presented by C. S. Colvin. It is interesting to note that the frequency of this disease, not uncommon in the United States, is about 1 to 100,000 in Australia. In the treatment of dendritic ulcer, Frank Phillips cleans the little knobs on the ulcer with a dental drill and uses dry blotting paper around the infected region to wipe off the epithelium. He then uses atropine and a bandage.

Lennox Price reported 2 consecutive cases of nonmagnetic metallic intraocular foreign bodies removed by means of forceps introduced into the vitreous. The first eye was saved without much vision, but the second eye was lost from panophthalmitis. R. G. Banks-Smith reported a case of partial thrombosis of the central retinal vein treated with dicumarol. The patient was admitted to the hospital, where the prothrombin time could be estimated. Three hundred milligrams of dicumarol was given as the initial dose; then 200 mg., for the next two days; then a dose of 100 mg. was repeated for a while. He stated the belief that this anticoagulation therapy prevented complete occlusion of the vessel.

Optic neuritis following measles was discussed by T. C. Meurer, with presentation of 3 cases. In all these cases disks were pale, but useful vision was finally obtained. Vision improved to 6/9 or better within twelve months.

Papers on orthoptics were read by Emmie Russell, J. A. Pockley and Diana Mann. Miss Russell stated the belief that the symptoms of the exophorias are easily relieved, that hyperphorias respond only fairly well and that the best results are obtained with convergence insufficiencies. Pockley stated: "Long-continued, uncontrolled treatment by the orthoptist can easily be an evil and I think many orthoptists will agree that an operation at the right time may shorten the period of treatment dramatically. Conversely, unexpected progress may cause the surgeon to modify or to abandon his plan for operation." Miss Mann stated the belief that normal binocular vision is developed in the first two years of life; if it is not developed then, no subsequent training can make amends. Any divergent squint, she asserted, tends to recur under certain conditions, and constant convergent squints are never corrected without operation.

Arthur D'Ombra discussed his personal experience with allergic sensitivity to procaine hydrochloride. He now uses as a substitute the following solution, which he finds effective and safe:

Cocaine hydrochloride .....	0.75%
Epinephrine chloride .....	1: 50,000
Chlorobutanol .....	0.50%

The final paper was a survey of ophthalmic diseases in western New South Wales, by K. B. Redmond. Forty-eight conditions were investigated in his preliminary survey. As might be expected, refractive errors were the most frequently observed, and after that, conjunctivitis, injuries, pterygium and strabismus.

This volume is additional evidence of the high level that has been attained by Australian ophthalmology.

G. M. BRUCE, M.D.

**Refraction of the Eye.** By Alfred Cowan, M.D. Third Edition. Price, \$5.50. Pp. 287, with 187 illustrations and 3 colored plates. Philadelphia: Lea & Febiger, 1948.

Dr. Cowan's "Refraction of the Eye" is so well known (ARCH. OPHTH. 34:172 [Aug.] 1945) that it needs no comment except to welcome its appearance in a third edition and to state that this new edition has been revised and brought up to date. The book merits its well deserved popularity; as a comprehensive and practical treatise, it is of great service to students of ophthalmology.

ARNOLD KNAPP.

**Collected Reprints from the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.** July 1945 to December 1947. Volume 8, Baltimore, 1948.

Volume 8 includes the reprints of the articles by the members of the staff of the Wilmer Ophthalmological Institute which appeared between July 1945 and December 1947; 50 articles and the titles of 12 other publications are listed. This imposing collection covers a wide range of subjects and exemplifies the industry and ability of this excellent group, working under the supervision of the director, Dr. Alan C. Woods.

ARNOLD KNAPP.

**The W. H. Ross Foundation (Scotland) for the Study of Prevention of Blindness.** London: University of London Press, Ltd., 1948.

This volume is a compendium of papers which have been published as the result of grants made by this foundation. The papers are of widespread ophthalmologic interest and for the most part have to do with injuries and infections of the cornea, especially those encountered in industrial practice. A list of the titles and their authors follows:

A. J. Rhodes: Conjunctival Bacteria and Hypopyon Ulcer  
Studies on the Bacteriology of Hypopyon Ulcer

R. M. Dickson: Traumatic Ulcer of the Cornea, with Special Reference to Coal Miners

First-Aid Treatment of Industrial Eye Injuries

Eye Injuries in Industry

A Statistical Analysis of Persons Certified Blind in Scotland

Dorothy Adams Campbell: Hereditary Microphthalmia in Albino Rats

Joseph R. Mutch and Donald Mackay: The Detection and Significance of Melanophore-Expanding Substance in Urine and Blood, with Special Reference to Retinitis Pigmentosa

J. M. Robson and G. I. Scott: Local Treatment of Experimental Pyocyanus Ulcers of the Cornea with Albucid Soluble

J. M. Robson and Walter Tebrich: Penetration of a Water-Soluble Sulphonamide (Albucid Soluble) into the Eyes of Rabbits

Penetration and Distribution of Sodium Sulphacetamide in Ocular Tissues of Rabbits



- J. M. Robson and G. I. Scott: Local Effectiveness of Sodium Sulphacetamide (Albucid Soluble) in Treatment of Experimental Ulcers of the Cornea  
Effect of Certain Chemotherapeutic Agents on Experimental Eye Lesions Produced by Staphylococcus Aureus  
Local Chemotherapy in Experimental Lesions of the Eye Produced by Staphylococcus Aureus
- J. M. Robson: Experimental Corneal Ulcers
- J. M. Robson and G. I. Scott: The Production and Treatment of Experimental Pneumococcal Hypopyon Ulcers in the Rabbit  
Experimental Streptococcal Lesions of the Rabbit's Eye and Their Treatment  
Proflavine and Corneal Injection
- M. Ginsberg and J. M. Robson: The Effect of Detergent on the Penetration of Sodium Sulphacetamide (Albucid Soluble) into Ocular Tissues
- T. P. Duguid, M. Ginsberg, I. C. Fraser, J. Macaskill, J. C. Michaelson and J. M. Robson: Experimental Observations on the Intra-Vitreous Use of Penicillin and Other Drugs
- Arnold Loewenstein and John Foster: Contribution to Knowledge of Ocular Siderosis and Posterior Degenerative Pannua

# ARCHIVES OF OPHTHALMOLOGY

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## OPHTHALMOSCOPY AND OPERATIONS FOR REDUCTION OF HIGH BLOOD PRESSURE

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HIGH blood pressure, a reflection of many underlying disease conditions, is prevalent and commonly fatal, but it is not in itself incompatible with a long and active life. The problem of caring for the afflicted has become so vital in the discussion of diagnosis and treatment that the literature on the subject is voluminous and repetition of outmoded methods for the recognition, alleviation and cure of this symptom frequently conceals the basic pathologic processes, without disclosing any beneficial therapy. In an aging population, in which the stresses and strains of life are increasingly evident in the violent conflicts of emotions and ideologies, the vascular system of man reflects the conditions under which he exists. In the medical world, this effect is most pronounced in what is designated as cardiovascular-renal disease.

The reactions to anxiety differ greatly. A given grade of vascular hypertension may produce a wide variety of symptoms and degrees of severity, more or less dependent on the age and sex, as well as on the peculiarities of the patient.

It has been well stated that "no one who has had any contact with hypertensive patients can escape the impression that heredity plays an important role in the production of high blood pressure."<sup>1</sup>

Perhaps few fields of ophthalmoscopic investigation have led to as many divergent, and sometimes contradictory, views as those concerned with "the fundus in hypertension." This lack of a uniform concept calls for simplification, rather than the advance of an elaborate system of grades. It is necessary to think of the pathologic changes in the fundus as a progressive process, neither constant as to duration nor regular in detail. If this is done, then a given pattern can be placed with some degree of accuracy as early or late, with the obvious intermediate gradations, or as rapid or slow in development. However, for this, a

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Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, Jan. 15, 1948.

1. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, *Arch. Int. Med.* **33**:343 (March) 1924.

thorough understanding and, above all, a competent recognition of the vessels of the fundus both in health and disease are prime requisites; parenthetically, it takes much time, critical inspection and a fine discriminating sense to differentiate correctly the physiologic from the pathologic signs.

Photographs of the fundus, when clear, sharply focused and including more than the nerve head and a small surrounding zone, supply information on which an elastic but uniform classification may be based.

Fralick and Peet<sup>2</sup> noted a frequent inability to differentiate angiospasm and early sclerosis of the retinal arteries. They stated the belief that the disappearance of the retinitis after lowering of the blood pressure through resection of the splanchnic nerves was evidence of an angiospastic, rather than an arteriosclerotic, lesion. They also stated that in most of their cases there was a combination of the two types. The more visible the sclerosis, the more difficult it was to demonstrate areas of localized angiospasm. They stated:

If it is agreed that retinitis develops in areas in which there has been long-standing severe angiospasm, then the localized areas of retinitis, characterized by edema and hemorrhage, must be recognized as being associated with local spasms of the retinal arteries, even though masked by sclerosis.<sup>2</sup>

The authors made reference to rapidly progressive arteriolar nephrosclerosis ("malignant hypertension") and called attention to the ineffectual medical treatment.

Cohen<sup>3</sup> reported:

Ophthalmoscopic diagnosis in cases of hypertensive disease requires a differentiation between arteriolar spasm and arteriolar sclerosis, which is an important but frequently impossible distinction.

Hallum<sup>4</sup> has recently suggested that when branches or portions of the arterioles show constriction without an increase, or indeed with a decrease, in the light reflex it is likely that angiospasm is present. Further, subsequent disappearance of these arteriolar constrictions is proof of their spastic nature, whereas if the constrictions persist or tend to increase permanent changes in the walls of the arterioles are indicated.

The ophthalmoscopic reports are not numerous but express the views of the reporters.

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2. Fralick, F. B., and Peet, M. M.: Hypertensive Fundus Oculi After Resection of the Splanchnic Sympathetic Nerves, *Arch. Ophth.* **15**:840 (May) 1936.

3. Cohen, M.: Ophthalmoscopic Changes Associated with Hypertensive Vascular Disease as a Guide to Sympathectomy, *Arch. Ophth.* **37**:491 (April) 1947.

4. Hallum, A. V.: Changes in Retinal Arterioles Associated with the Hypertension of Pregnancy, *Arch. Ophth.* **37**:472 (April) 1947.

5. Footnote deleted by author.

A careful estimation of the grade of sclerotic changes in the retinal arterioles was suggested by McKeown.<sup>6</sup> Gans<sup>7</sup> proposed a classification with two parallel groups of signs: on one side, those emphasizing the sclerosis and, on the other, the arteriolar constriction, the retinopathy and the retinopathy with papilledema.

Friedenwald<sup>8</sup> called attention to the changes associated with senescence and concluded that in the early stages of hypertensive vascular disease without atherosclerosis the visible portions of the retinal arterial tree are either normal or, in some cases of the severest form, dilated, and he suggested that one should not overestimate the reliability of the ophthalmoscopic findings in the diagnosis of senescence.

He stated that many cases of atherosclerosis are uncomplicated by hypertension. In discussing the arteriolosclerotic process of hypertension, he stressed age and called attention to the fact that most patients with arteriosclerotic hypertension are over 60 and few under 50 years of age, whereas most of the patients with nonatherosclerotic hypertension have the onset of their hypertension under the age of 50 and have well developed signs of hyaline changes in the retinal arterioles before they reach 60. Patients under 40 or over 60 years of age present no serious difficulties in the differential diagnosis of these forms, but the 40 to 60 year age group represents an important fraction of the patients for whom the differential diagnosis must be made. He asserted that in patients over 60 with moderate, fixed hypertension the retinal vessels are almost always narrow and straight and branch at acute angles. There is a question in my mind whether the last statement is correct. It is certainly not borne out by my photographic records. More often than not, the vessels do not alter their course.

Tooke and Nicholls<sup>9</sup> stated:

. . . by and large, this operation [splachnectomy] is disappointing in its effect on the blood pressure level, but nevertheless, the patients are improved, when one takes into consideration symptoms and fundus findings.

A careful review of the published reports regarding surgical treatment leaves one in a state of confusion. This, however, is less marked if the perusal of papers is limited to those that have appeared in the past few years, in which, because of the more discriminating selection

6. McKeown, H. S.: Ocular Fundi in Essential Hypertension, Pre- and Post-Operative, New York State J. Med. **44**:2692 (Dec. 15) 1944.

7. Gans, J. A.: Classification of the Arteriosclerotic Hypertensive Fundus Oculi in Patients Treated with Sympathectomy, Arch. Ophth. **32**:267 (Oct.) 1944.

8. Friedenwald, J. S.: Disease Processes Versus Disease Pictures in Interpretation of Retinal Vascular Lesions, Arch. Ophth. **37**:403 (April) 1947.

9. Tooke, F. T., and Nicholls, J. V. V.: Changes in the Fundus Oculi Following Splachnectomy for Malignant Hypertension, Canad. M. A. J. **41**:21 (July) 1939.

of patients and the more refined operative procedures, the results reported are more satisfactory to the patient and more satisfying to the surgeon.

If a complete physical examination reveals that the condition of the patient is favorable and if the findings in the fundus are to be the deciding factor for or against operation, the question is, "Are we as ophthalmologists prepared to give a detailed report of the ophthalmoscopic picture and, on the basis of that design, render a verdict for or against surgical intervention?" This responsibility is not only grave, but one calling for a high degree of knowledge and skill. This presentation emphasizes that the ophthalmoscopic picture is an important element in correctly estimating the advisability of a pressure-reducing operation.

At the beginning of any consideration of hyperpiesia it must be understood that the vast majority of patients with hypertension present no lesion of the fundus. This statement cannot be repeated too often. After a variable time, often several years, during which period the blood pressure may be extremely high, the earliest changes suggestive of hypertension appear. These signs are identical with those in the retinal vessels of elderly patients and consist in slight narrowing of the arteries with or without faint indentations of the veins where they are crossed by the arteries. The indentation of veins is not pathognomonic but only suggestive. Incidentally, it is time that the expression "nicking" be abolished as incorrect. Subsequently, there is an intensification of all signs, not a distinguishable stage, but an almost imperceptible accentuation, in which the arteries may become more tortuous in portions of the retinal tree or be limited to the macular region. Later, there are slightly increased arterial reflexes, elevations or compression of veins where they are crossed by the arteries and superficial streak hemorrhages. The vessels may be of uneven width and occasionally exhibit a genuine, visible spasm—contraction of one or more arteries. No exudates are present. Still later, the fundus signs are definitely those of retinopathy, with hemorrhages, exudates and increased involvement of the arteries. The pattern changes with time as a few exudates and large superficial hemorrhages appear, with marked increase in the light reflex from the arterial wall, a high grade of sclerosis, with white vessel walls, and deep indentations of the veins.

The nerve head may be swollen—papilledema. This mere statement is not sufficient, for the disk may not only be elevated but may have many new vessels on its surface and newly formed vessels in front of it, or it may be combined with hemorrhages in the vitreous, retinitis proliferans and adventitious new-formed vessels in the retina with large, pale areas of exudate or a macular star. In some cases the edema of

the nerve head may dominate the picture. This is indicative of increased intracranial pressure. To exclude an expanding growth may be so difficult that only by careful neurologic and roentgenographic examinations and a correlation of all the facts can a final opinion be rendered. It has been proved that retinal edema always precedes the macular star and that later the radiations of the star decrease in width and length until only a few small, radially arranged spots remain. Occasionally, if the patient lives long enough, even these disappear. The soft, gray retinal area, of variable size, commonly more or less rounded and overlying a retinal vessel, has been called a cotton wool patch. This sign is of great clinical significance, for it usually, although not invariably, indicates vascular deterioration. In some cases these alterations progress rapidly.

As the concluding phase of the disease is approached, more hemorrhages and more cotton wool patches appear; or neuroretinal edema with a macular star, detachment of the retina and other changes may develop.

Edema of the retina is commonly considered evidence of conversion from the benign to the terminal stage. It must be noted, however, that remissions can occur. Further, in many cases of the atherosclerotic type, a fulminating retinopathy never develops, but the patient dies of a cerebral or cardiac accident. Retinal hemorrhages, cotton wool spots and neuroretinal edema may be absorbed spontaneously. This possibility must constantly be kept in mind when one is evaluating therapeutic benefits. The importance of this warning is realized in the review of reports in which the disappearance of transitory signs is stressed as the direct result of operation. It is common knowledge that such signs frequently vanish without any medical treatment or surgical intervention.

Just when in this progressive disease should the ophthalmologist recommend operation, or even sanction it? If the surgeon concludes that the patient's condition warrants operation and the ophthalmologist has found no signs of retinopathy, there should be no delay. If the surgeon has decided to operate and asks only for a confirmatory opinion, the ophthalmologist will be derelict in his duty to the patient if, when he finds signs of fulminating retinopathy or papilledema, he does not report that there is little likelihood of prolonged benefit from operation. The obligation is of the utmost gravity and must be assumed if the patient who might be helped is to be given a chance, whereas the patient with terminal retinopathy is protected by his surgeon's vigorously opposing an operation.

Information of value may be gained from the observations presented in a few cases.

## REPORT OF CASES

CASE 1.—A professional man aged 48 had, in 1941, normal fundi, with normal vision and a systolic pressure of 152 mm. Four years later, in 1945, without his having had any intercurrent infection, his systolic pressure was 220 mm., and he had one small, superficial retinal hemorrhage. A comparison of his fundus pictures showed little compression of veins and no visible alteration in the course or caliber of the retinal vessels.

Ten months later, his blood pressure was 245 systolic and 110 diastolic. Operation was performed by Dr. R. H. Smithwick in March 1945, first, on the right side and, two weeks later, on the left. The patient's physician, Dr. A. M. Yunich, reported: "On Oct. 26, 1945, he weighed 173 pounds (78.5 Kg.) and showed decided improvement, both mentally and physically. He had no complaints, and his blood pressure was 152 systolic and 90 diastolic when he was in the standing position without his belt. The urine had a specific gravity of 1.009 and was negative for albumin and sugar; microscopic examination revealed no abnormal constituents.

"On Jan. 30, 1946, the urine had a specific gravity of 1.015 but was otherwise not remarkable. The patient weighed 176 pounds (79.8 Kg.), and his general condition was excellent, even though his blood pressure had risen to 190 systolic and 100 diastolic.

"When last examined, in April 1947, he weighed 185 pounds (83.9 Kg.), and his general condition was remarkably good. He was working regularly and was in the best of spirits. He had no headache, dizziness, visual disturbances or precordial distress, such as he had been troubled with prior to operation. The most amazing clinical finding, however, was a rise in his blood pressure to the pre-operative level of 210 systolic and 120 to 130 diastolic."

He was comfortable and was carrying on his professional activities. He had no retinal hemorrhages, and both the arteries and the veins were smaller than before operation. From the ophthalmoscopic standpoint, his was an excellent case for operation, for the changes in the retinal vessels were minimal.

CASE 2.—A married woman aged 29, on examination to determine the cause of pain in the occipital region, was found to have a systolic pressure of 200 mm.

The retina was clear, with no edema; the temporal half of the disk was flat; the nasal side was thick. The veins were slightly dilated throughout their course. The light reflex from the superior temporal artery was increased, and the width of the blood column was variable. In the left eye, the disk was outlined throughout its circumference; the retinal striations were defined; the veins were normal in size, and there was only slight narrowing of the arteries; many large vitreous reflexes partly concealed the vessels. The appearance of the fundi suggested hypertension.

Two years later, Dr. James L. Poppen saw the patient and made the following report:

"The average blood pressure was 240 systolic and 136 diastolic. There was no evidence of widespread vascular disease, although there was some decrease in renal function, as well as in the phenolsulfonphthalein output. The intravenous pyelograms were within normal limits. The urine concentrated to 1.026, with a slight trace of albumin; the nonprotein nitrogen measured 31 mg. per hundred cubic centimeters. The general blood picture was normal. Roentgenograms of the chest revealed only slight cardiac hypertrophy.

"On May 13, 1939, splanchnic resection, lumbar sympathectomy and nephro-omentopexy were performed on the left side. On May 23, a splanchnicectomy,

subdiaphragmatic, and lumbar sympathectomy were executed on the right side. The patient had a right hemiplegia while in the hospital; this cleared up to some extent, but she was left with slight aphasia. Her blood pressure dropped considerably at this time, and within six months it was back to its usual level."

At this time the fundi showed no perceptible change except that the nasal side of the right disk was flatter than the temporal and the margin was visible. Five years later, the margin of the disk was perfectly distinct, the arteries were uniformly narrow and the veins were less distended.

At no time did the patient have any evidence of retinopathy. She had a cerebral accident and died July 20, 1945. For six years she was practically free from symptoms and carried on her usual household duties. Her fundi reflected this favorable outcome.

CASE 3.—F. H. was first examined on Oct. 18, 1943, at the age of 34. His complaint was difficulty in focusing for near work, and the only noteworthy item in his history was the occurrence of a cerebral hemorrhage in 1941, when his blood pressure was 270 mm. systolic.

Vision was 6/7.5 in each eye. The disks were clearly and distinctly outlined. There was some compression of the full retinal veins, and in the left eye a few round, granular retinal hemorrhages were noted.

In November 1943, Dr. David P. Boyd performed a Smithwick<sup>10</sup> transdiaphragmatic splanchnicectomy on the right side. The patient had a stormy convalescence, and the operation on the left side was not done until June 1944.

Dr. Boyd reported: "The patient's blood pressure showed a fair drop, although it fluctuated widely, at times being 140 and at others 210 mm., but never reaching the preoperative level. He had a smooth convalescence from the second operation."

The last photographs of the fundus were made on March 15, 1945, at which time there was a slight decrease in fulness of the veins and the arteries were narrower. Vision was 6/6 in each eye. In his latest report, of May 8, 1947, the patient stated: "I am feeling well. I have little trouble with my eyes; but it is rather difficult to concentrate, and my memory is poor." He has been fairly comfortable for four years.

CASE 4.—A woman, aged 40, in 1932 had frequent frontal headaches, which were most intense in the morning; she experienced considerable fatigue after reading and became sleepy on the least concentration on near work.

Vision in the right eye was 6/30 without glasses and 6/15 with correction. The fundus was normal, and the poor vision was the result of dense corneal opacities. Vision in the left eye was 6/6. The fundus was normal; the disk was sharply and clearly outlined, and the vessels were normal.

A year and a half later the headaches were said to be much worse. Physical examination revealed nothing significant except for the blood pressure, which was 180 systolic and 110 diastolic. The family physician placed her under medication. The fundi at this time showed slight narrowing of the retinal arteries and a faint haze in the retina.

She was not seen again until several years later, at which time the pressure was 240 systolic and 130 diastolic. There were marked irregularity in the caliber of the arteries, slight but measurable dilatation of the retinal veins and one streak hemorrhage. A splanchnicectomy was advised.

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10. Smithwick, R. H.: *Surgery of the Sympathetic Nervous System*, New England J. Med. **224**:329 (Feb. 20) 1941.



The following year, she had a Smithwick splanchnicectomy on the right side, and four months later a similar operation on the left side. After each operation she had pleurisy and an excessive amount of pain and was extremely uncomfortable and very short of breath. A year and a half later her fundi showed no notable change except that the superficial hemorrhage had disappeared.

Now, nearly two years after operation, she is still short of breath but has little headache and feels decidedly better, although her pressure is stabilized at 200 systolic and 120 diastolic.

This case is one in which the ophthalmoscopic findings suggested a satisfactory result.

CASE 5.—A married woman aged 49, without general infection of any kind, had a systolic pressure of 218 mm., for relief of which she had been taking drugs for one month. Urinalysis and tests of renal function gave normal results. Her only complaint was pain in the left eye.

Vision in the right eye was 6/12 without correction, and 6/5 with a minus sphere. The retinal veins were uniformly dilated but not tortuous. The arteries were of uneven caliber and presented several frank spasms—contractions without evidence of changes in the vessel walls. There were increased tortuosity of the superior temporal artery; faint, but definite, retinal edema and a few round granular, deep retinal hemorrhages.

Vision in the left eye was 6/6. The disk was clearly outlined through slight retinal edema. The veins were straight and fuller than normal. The inferior branches of the arteries were tortuous. Several definite arterial spasms and some granular, deep red retinal hemorrhages and superficial streaks of blood were observed.

The patient had a bilateral Smithwick operation and died shortly thereafter.

In this case, the vascular changes were danger signs, the serious import of which should have been recognized and operation postponed indefinitely.

#### COMMENT

The majority of hypertensive patients are free from symptoms, and the high blood pressure is discovered on routine physical examination. The ophthalmologist often makes the original diagnosis of hypertension and inaugurates the investigations which may lead to an operation. The prime symptom for which he is consulted is an intense, persistent, treatment-resisting, generalized headache, or nuchal, occipital or frontal distress, frequently most intense in the early morning hours. Because of visual defects a patient may visit the ophthalmologist, who recognizes the causative significance of the vascular changes, the congestion of the fundus, the lack of retinal definition, the retinal hemorrhages, the retinopathy or the papilledema.

The ophthalmologist should be able to state with reasonable certainty whether a given fundus pattern indicates a favorable postoperative outcome, one of doubtful value or a disappointing result. He must know the life history of the retinal variations and estimate the life expectancy of the individual patient. He should render a concise, but genuinely explanatory, report, including an opinion based on knowledge of the favorable and unfavorable results following operation and on

understanding of the fundus signs. If this is done, more patients with a good prognosis will be operated on, and fewer of those with hopeless disease will be subjected to the trying ordeal, from which little or no benefit can be expected. The prognosis is based on the state of the retinal vessels.

The ophthalmoscopic signs which determine the feasibility of operation are correlated. Many exceptions may be made to them, and occasionally a patient with what seems to be a hopeless condition may, by operation, be given a few more years of life.

It must be remembered that hypertension is a complex manifestation of many factors, all of which must be evaluated before an accurate prognosis can be given. All advice is predicated on the integrity of the kidneys, the heart and the cerebral vessels.

From the ophthalmoscopic standpoint, there are two types of hypertension. In one there are very slight vascular changes, even after many years of high pressure. Eventually, the majority of patients die of a cerebral or cardiac accident without ever having had a retinopathy. The other, rapidly progressive arteriolar nephrosclerosis (so-called malignant hypertension), should be called fulminating because of the rapidly progressing retinopathy. Frequently, at the time of the initial examination, there are extensive exudates and hemorrhages, with or without retinal edema and an irregular outline of the blood column, spasm or white-walled sclerotic vessels. The fulminating type is comparatively seldom engrafted on the simple form of hypertensive vascular disease. There is, however, no definite duration of the benign stage and no reliable guide by which one can predict the imminence of the signs which almost invariably foretell an early death. It is to cases of this potentially fulminating type that the surgeon's attention is often directed, for without help the patient is doomed. As a last resort, an operation may be tried, for medical treatment is ineffective.

The severe cases of retinopathy are usually associated with signs of advanced renal dysfunction, so that the patient rarely reaches the standard of renal efficiency demanded by the most careful surgeons. Patients with papilledema and extensive neuropapillary edema should not be subjected to operation.

#### SUMMARY

If the patient has no serious involvement of the heart, kidneys or cerebral vessels and no retinopathy, the ophthalmologist can sanction operation.

If a retinopathy is present, with cotton wool patches, hemorrhages and exudates, approval may be given only when the results of physical and laboratory tests seem to warrant an operation, with the expectation that life will be lengthened.

If the patient has definite arteriosclerosis, as indicated by white-walled vessels; if he has round, deep, red, granular retinal hemorrhages; if there is considerable retinal edema, as evidenced by a decrease in the visibility of the retina, or if there are intense, widespread edema of the retina and obscuration of the margins of the disks, with or without newly formed vessels on or about the disk, operation is contraindicated. If he has had recent closure of a retinal artery, with the typical white edema in the region supplied by the closed vessel, or sudden occlusion of the central vein, operation should not be attempted.

If there is marked papilledema with narrowing of the arteries or fulness of the veins, operation should be opposed unless there are extenuating circumstances, at which time the surgeon assumes the responsibility and the patient understands the risks, for it is improbable that life will be materially prolonged by surgical intervention.

In addition to these sharply and clearly defined exceptions, there are many patients with little retinal edema, but with large, greatly indented veins and uneven lumen of the vessels. Such patients are poor risks.

Finally, if the patient with hypertension is to be made comfortable, his anxieties must be relieved and his fear of imminent disability or death dispelled.

344 State Street.

# ELECTRONIC FLASH (GAS DISCHARGE) TUBE IN PHOTOGRAPHY OF THE ANTERIOR SEGMENT OF THE EYE

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AND

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SOME of the special requirements for illumination in photography of the anterior segment of the eye appear to be met more satisfactorily by a recently developed type of light source than by methods previously employed. For several reasons, in ocular photography it is expedient to have the camera relatively close to the eye. But the different distances of various structures of the eye, especially of its adnexa, from the camera make it necessary to use rather small lens apertures to obtain sharp definition. The small aperture of the diaphragm necessitates high levels of illumination for adequate exposure of the film.

With a lens aperture of  $f/2.8$  a segment of the eye 5 mm. in depth is in fair focus, while with an aperture of  $f/16$  a segment 20 mm. in depth is in comparable focus and the sharpness in the midrange is, of course, significantly improved. Because of the sensitivity of the eye to light and difficulty in holding the eye still, a short time of exposure must be employed to reduce discomfort and to "stop" any motion.

Two commonly employed sources of illumination for external ocular photography are flash bulbs, which contain combustible metal foil or wire, and overloaded incandescent filament lamps, commonly known as "photofloods." Flash bulbs give the necessary intense light, but are currently in short supply, are relatively expensive and must be replaced for each picture. Furthermore, an unpleasant blast of heat is felt by the patient when the flash bulb is placed in the photographically most desirable position. "Photofloods" are less satisfactory. Although they are frequently used in conjunction with a resistance, so that the camera may be focused in diminished light, in an attempt to lessen the patient's discomfort from heat and glare, the photophobic eye is still uncomfortable during focusing. Lacrimation is often excessive, producing highlights which detract from the picture. During exposure of the film, the resistance is removed by a switch, permitting the bulbs to

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light to their full brilliance; this flood of light is even more uncomfortable, and yet is of insufficient intensity to permit stopping down the lens adequately unless several lamps are used, with consequent increase in the number of corneal reflections.

Some of the defects of the illuminants already discussed have been overcome in a photographic arrangement utilizing an electronic flash (cold cathode gas discharge) tube. This tube contains one of the rare gases, which is caused to ionize by a high voltage discharge, producing light with a color temperature of about 6,500° K., suitable for use without filters with daylight "kodachrome" or "ansco" film. The flash is of high intensity but of brief duration, approximately 0.0001 second, and is remarkably cool, so that discomfort to the patient is at a minimum. The lacrimation and photophobia produced by "photo-floods" and ordinary flash bulbs are notably absent.

The gas discharge tube has previously been used for ocular photography in an apparatus specially designed for photographing conjunctival and corneal vessels at considerable magnification.<sup>1</sup> While this apparatus is suitable for investigative work, a simpler arrangement, which may be used with ordinary types of cameras, is convenient for routine external ocular photography in the office or clinic. This arrangement can be operated quickly and easily by a nurse or secretary after a few minutes' instruction.

For use in routine photography of the anterior segment, the electronic flash tube is provided with a handle, reflector and a cone-shaped shield, as pictured in figures 1 and 2. A 75 watt, filament type projection bulb for illumination of the eye during focusing is mounted inside the shield, directly in front of the flash tube. At the small end of the cone is placed a piece of nearly colorless, heat-absorbing glass; this is not essential but adds to the patient's comfort by reducing to a minimum the heat from the projection bulb. The entire unit is flexibly supported alongside the camera, and as near to it as possible. The shield surrounding both lights serves to limit the emission of light to a beam only slightly larger than the desired photographic field. In this way, a spot of light is furnished from the continuously burning filament source, permitting accurate direction of the light toward the eye. When the discharge tube is flashed, the operator, patient and camera lens are protected from all light not actually directed at the eye to be photographed.

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1. Gartner, S.: Blood Vessels of Conjunctiva: Studies with High Speed Macrophotography, *Arch. Ophth.* **32**:464 (Dec.) 1944. Pearce, cited by Tisdall, F. F.; McCreary, J. F., and Pearce, H.: The Effect of Riboflavin on Corneal Vascularization and Symptoms of Eye Fatigue in R. C. A. F. Personnel, *Canad. M. A. J.* **49**:5 (July) 1943.

Sufficient light to permit stopping down the camera lens to  $f/16$  with color film is obtained when the flash tube is located 12 inches (30 cm.) from the eye (the small end of the cone is thus 4 inches [10 cm.] from the eye, or directly beside the camera lens) and is

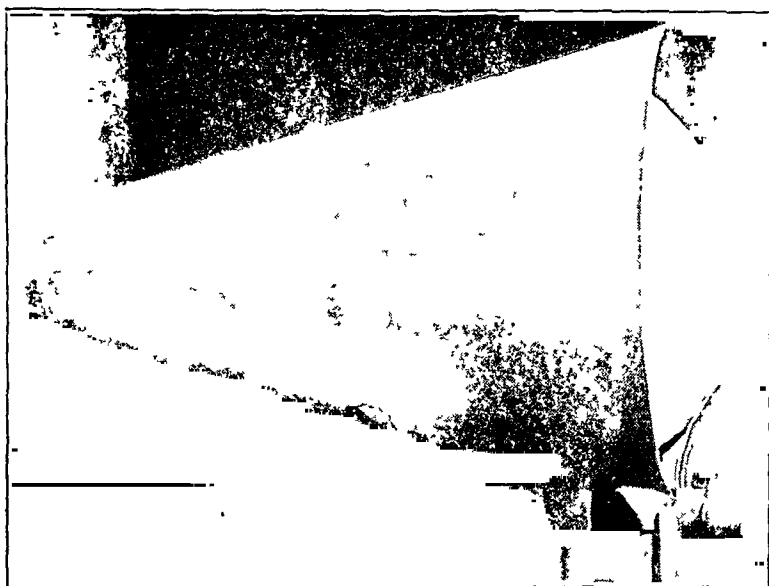


Fig. 1.—Photograph of cone-shaped shield, containing focusing light in center, and electronic flash tube just in front of the reflector.

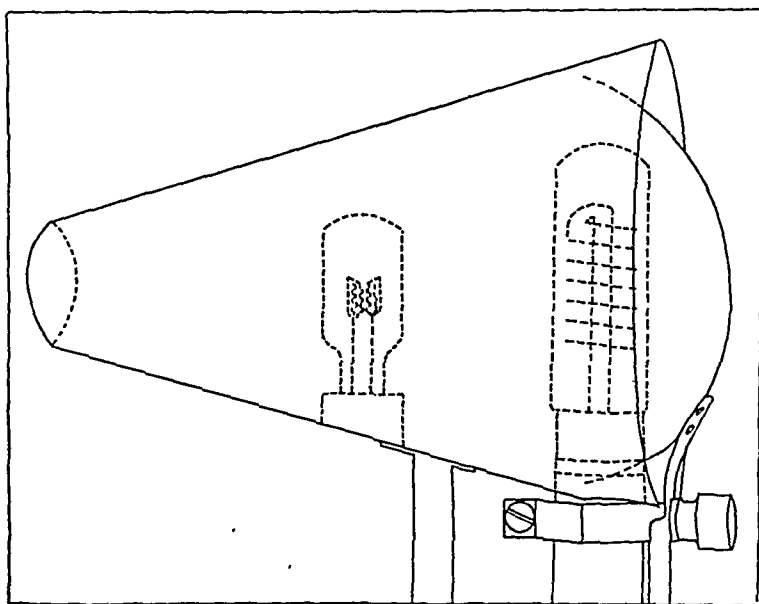


Fig. 2.—Schematic diagram of the apparatus shown in figure 1.

operated at maximum output by an appropriate power supply. It has been found satisfactory to employ flashes of an intensity of the order of 50,000,000 lumens and a total light output of 9,500 lumen seconds. For this purpose, the flash tube has been energized by a pair of 30 microfarad condensers, which are charged to 2,500 volts by a simple

transformer-rectifier circuit providing 200 watt seconds of energy per flash. Reputedly, the flash tube can be discharged at intervals of thirty seconds for more than 10,000 flashes. Electronic flash power supplies with characteristics similar to this laboratory-developed unit are available commercially.

No mechanical synchronization of the shutter with the flash is necessary, although this would be a convenience. The camera may simply be set on bulb, the shutter opened, the flash activated by pressing a small switch and the shutter closed. Depending on the speed of the operator's fingers, the shutter probably remains open upward of one-half second. Although the focusing lamp is permitted to burn continuously and the room is not darkened, this incidental illumination is of such relatively low intensity that it does not produce, either before or after the flash, any appreciable modification of the image recorded during the flash. The only perceptible image is recorded during the very brief flash, so that ocular motion does not interfere and blinking has been found to present no problem.

Experimental investigation of possible harmful effects to the eye from exposure to the electronic flash was carried out before its use on patients. Several volunteers were exposed to series of at least twenty flashes during ten to fifteen minutes. No discomfort or disturbance of vision was noted by them at any time after disappearance of the after-image of the light source.

#### SUMMARY

For photography of the anterior segment of the eye, an electronic flash tube of 9,500 lumen seconds' output provides more satisfactory illumination than the illuminants in common use for this purpose, permitting life-size color pictures to be taken at a desirably small lens aperture, yet with relatively little discomfort to the subject. A special flash tube holder, with an additional filament source for focusing, facilitates the procedure.

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# ESTHETIC CORRECTION OF UNILATERAL ANOPHTHALMOS BY OPHTHALMOPROSTHESIS

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**A**NOPHTHALMOS was defined clinically by Mann<sup>1</sup> as a condition in which no eyeball, however small, can be found in the orbit. In life it would obviously be impractical to distinguish between true anophthalmos and an extreme degree of microphthalmos, for the matter could be determined only by microscopic examination of serial sections of the orbital contents. This would be of small clinical importance, even though the theoretic aspects are interesting.

## ETIOLOGY

May<sup>2</sup> stated that congenital anomalies of the eyeball are rare and may be bilateral. In anophthalmos the eyeball is replaced by a small solid or cystic mass. Parsons<sup>3</sup> stated the belief that even though the eyeball may apparently be absent (congenital anophthalmos) there are always microscopic vestiges of ocular tissues. In Berens' textbook,<sup>4</sup> congenital abnormalities are classified as (1) those due to errors of development, which may occur at any stage in fetal life, e. g., anophthalmos, microphthalmos and coloboma of the uveal tract, and (2) those due to intrauterine inflammation. The role of intrauterine inflamma-

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From the Richmond Freeman Memorial Clinic, a unit of the Children's Medical Center, affiliated with the Southwestern Medical Foundation.

1. Mann, I.: Developmental Abnormalities of the Eye, *Brit. J. Ophth.* **65**: 72, 1937.

2. May, C. H.: *Manual of the Diseases of the Eye*, Baltimore, William Wood & Company, 1941.

3. Parsons, J. H.: *Diseases of the Eye*, New York, The Macmillan Company, 1942.

4. Berens, C.: *The Eye and Its Diseases*, Philadelphia, W. B. Saunders Company, 1938.



tion has been denied; however, apart from other evidence, the microscopic appearance in such conditions as congenital anterior staphyloma and macular coloboma so closely resembles that found as a result of inflammatory lesions during extrauterine life that it is reasonable to assume a similar cause.<sup>5</sup>

Atkinson<sup>6</sup> reported congenital absence of the lacrimal gland in conjunction with anophthalmos; however, such a defect is an ophthalmologic curiosity and is seldom encountered, though its occurrence has been verified by postmortem examination. While some authors claim the existence of anophthalmos as an entity, others believe it to be only a more pronounced degree of microphthalmos. However, it has been noticed that the anomaly known as anophthalmos is usually bilateral and that microphthalmos is nearly always unilateral. Both conditions are believed to be the result of a failure of closure of the optic vesicle.

In cases of microphthalmos a cyst of the lower eyelid which contains a rudimentary eye is nearly always found. In almost all cases other congenital stigmas are seen, of which a miniature orbit is the commonest. Other defects, in the order in which they occur, are harelip, cleft palate, nasal cleft, supernumerary auricle and supernumerary digits. Some observers claim that associated deformities are less frequent in cases of microphthalmos than in cases of anophthalmos.

Microphthalmos has been described as a uniocular congenital deformity in which lack of development of one eye is in striking contrast to the development of the other. In some cases it may be said that the eye is not present at all, though a firm cystic tumor occupying the normal site of the eye in the orbit has sometimes been mistaken for an eye. Fuchs<sup>7</sup> described such a cyst as being attached to the lower lid, where it is seen glimmering with a bluish luster. When opened, the cyst is seen to contain a rudimentary retina, floating in a serous fluid. In cases of less marked deformity, coloboma, or congenital fissure of the iris and of the optic nerve, is usually present.

#### INCIDENCE

Anophthalmos occurs in man as a rare abnormality. In the literature, Collins<sup>8</sup> found only 30 cases of bilateral and 12 of unilateral anophthalmos, most of which were doubtful, as microscopic examination

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5. Parsons, J. H.: *The Pathology of the Eye*, New York, G. P. Putnam's Sons, 1906.

6. Atkinson, D. T.: *External Diseases of the Eye*, ed. 2, Philadelphia, Lea & Febiger, 1937.

7. Fuchs, E.: *Textbook of Ophthalmology*, translated by A. Duane, Philadelphia, J. B. Lippincott Company, 1924.

8. Collins, E. T.: On Anophthalmos, *Ophth. Hosp. Rep.* **40**:429, 1886-1887.

was not made. Von Hippel<sup>9</sup> stated that the recorded number of cases of bilateral anophthalmos was 64 and that of unilateral anophthalmos 23, in 15 of which there were congenital anomalies. Sex incidence was not significant, and heredity was a rare factor. Collins<sup>8</sup> and Gallemaerts<sup>10</sup> noted that in the rare familial and hereditary cases the condition was obviously germinal in origin and in several of these it was unilateral. Other abnormalities were not present in most cases.

#### CORRECTION

A search of the literature showed no previous reports on attempts at esthetic correction of anophthalmos. In previous cases of loss of an eye in infants and children one of us (P. J. M.) had restored the defect by ophthalmoprostheses, using the technic evolved while on duty at the United States Naval Dental School, the National Naval Medical Center, Bethesda, Md.<sup>11</sup> A number of naval personnel presented loss of an eye, the result of violent trauma, with destruction of areas of the lids and with redundant tissue in the cul-de-sac, so extensive that it was difficult to obtain retention of any type of prosthesis. These patients had received their injuries weeks, and even months, previously but had been unable to have the prosthesis made because of body wounds. Experience gained in obtaining an impression of the existing cul-de-sac, increasing its size by having the patient wear a prosthesis and then polymerizing ("curing") a larger prosthesis to replace the first was of great value in approaching the problem of miniature cul-de-sacs found in anophthalmos.

A girl aged 7 months (fig. 1 *A* and *B*), after a thorough physical examination, was referred to the department of ophthalmology. A careful clinical examination did not disclose any evidence of remnants of the eye and, in the absence of microscopic biopsy, it may be assumed that a true anophthalmos existed. The cul-de-sac was so small that it was necessary to use a 20 cc. hypodermic syringe for injecting the impression material into the orbital socket. The first working cast shown in figure 2 indicates the miniature size of the cul-de-sac. From the cast a wax pattern was made; and after it was tried in the orbital socket, it was invested and "cured" into scleral material, as described in previous articles.<sup>11</sup>

This "cured" sclera was then polished and placed in the orbital socket. It was necessary to tape the eyelids in order to maintain the prosthesis within the socket, as the muscles of the lid had little tone and were poorly developed physiologically.

9. von Hippel, E.: Anatomische Untersuchungen über angeborene Korektopie, *Arch. f. Ophth.* **51**:132, 1900.

10. Gallemaerts: Anophthalmia congenitale et familiale, *Ann. d'ocul.* **40**:490, 1924.

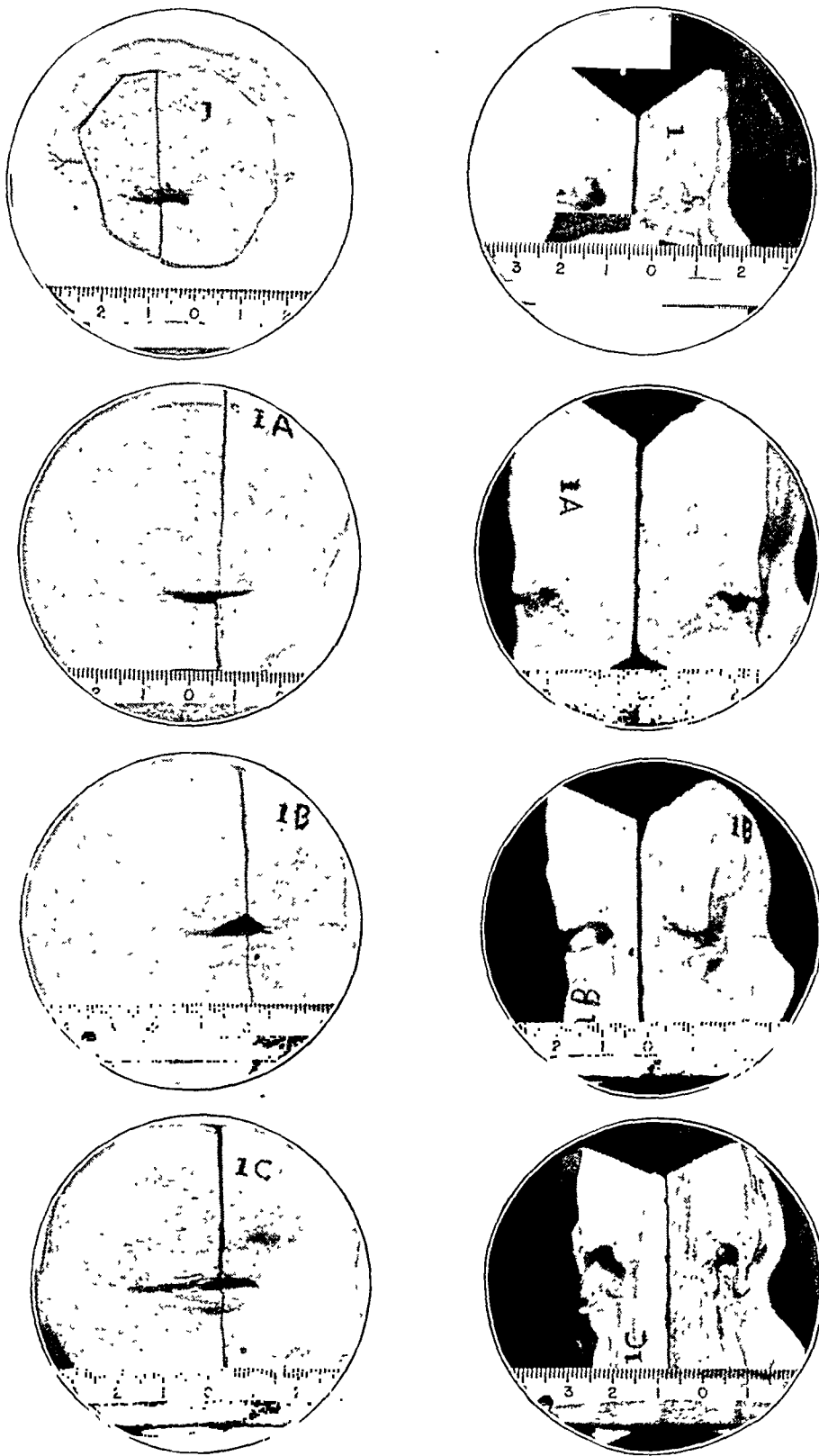
11. Murphy, P. J., and Schlossberg, L.: Eye Replacement by Acrylic Maxillo-facial Prosthesis, *U. S. Nav. M. Bull.* **43**:1085, 1944; *Mil. Surgeon* **96**:469, 1945. Murphy, P. J.; Pitton, R. D.; Schlossberg, L., and Harris, L. W.: Development of Acrylic Eye Prosthesis at the National Naval Medical Center, *J. Am. Dent. A.* **32**:1227, 1945.

Within a week the prosthesis was retained within the orbital socket without taping, and the patient was seen at regular weekly and biweekly intervals, as in orthodontic therapy. At these times the prosthesis was removed and the orbital socket thoroughly irrigated with isotonic sodium chloride solution, and the prosthesis was polished with prepared chalk and soft rag buffing wheels. Then, either it was reinserted or wax was added to the areas where growth seemed



Fig. 1.—*A* and *B*, infant girl aged 7 months. *A*, collapsed upper lid and miniature cul-de-sac; *B*, profile showing failure in growth of orbital area, which would not develop further without physiologic function. *C* and *D*, infant after twelve months of treatment, showing growth of the upper lid and orbital fissure; *D*, a profile, shows filling out of the orbital area with normal curvature of the lid cilia.

to have occurred within the socket. This prosthesis was worn for several days with the wax attached, after which it was removed and reinvested in a flask, and clear acrylic was added to replace the waxed areas. The prosthesis was then polished and reinserted and worn again for a week, or for a longer period.



Fif 2.—Series of working casts. (I) Cast made Jan. 18, 1946: cul-de-sac approximately 9 mm. wide, 6 mm. deep and 5 mm. in vertical diameters; (IA) cast made May 17, 1946: cul-de-sac approximately 12 mm. wide, 10 mm. deep and 8 mm. in vertical diameter; (IB) cast made Sept. 13, 1946: cul-de-sac, approximately 15 mm. wide, 11 mm. deep and 10 mm. in vertical diameter; (IC) cast made Jan. 25, 1947: cul-de-sac approximately 19 mm. wide, 12 mm. deep and 16 mm. in vertical diameter.

It soon became evident that new working casts were necessary in order to keep pace with growth changes within the cul-de-sac. These were made at regular intervals, as shown in figure 2, and new wax patterns were made from them, to be "cured" in scleral acrylic and then worn as before. Figure 3 shows four of these prostheses, with the changes in growth and shape apparent.

At the end of twelve months of treatment, as shown in figure 1 C and D, the greater lid and the orbital fissure had approached the normal. In the profile of the face, a filling out of the orbital area, with normal curvature of the cilia of the lid, is definitely perceptible.

The psychologic effect observed during the period of growth stimulus of the orbital area and after the prosthetic restoration of the eye was very noticeable in this child. Even allowing for the prejudice of the parents, there was a definite improvement. The parents and relatives living with her were enthusiastic over the betterment in her social relations with other children during play periods. For example, the parents reported that before treatment was begun the neighborhood children referred to her as "that one-eyed baby." After sufficient space in

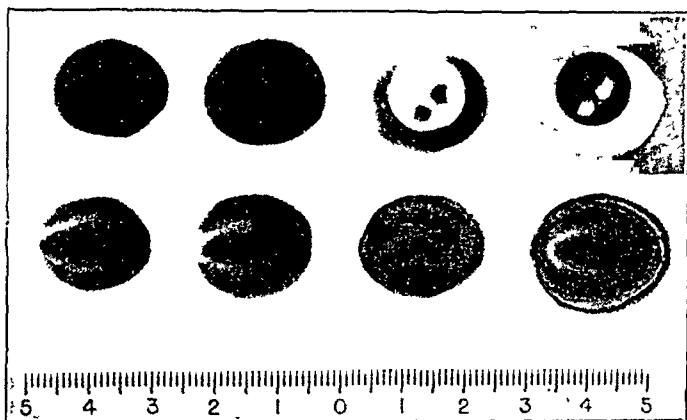


Fig. 3.—Upper figure: Four prostheses were inserted at intervals until the size of the sclera allowed for inlay of an iris. Lower figure: Growth of the cul-de-sac is apparent from this view of the posterior surfaces of the prostheses.

the cul-de-sac had been obtained to insert an iris in the prosthesis, the children only occasionally used this designation in referring to her. The parents moved into another neighborhood and in this new environment she was accepted without reference to her ocular anomaly. The child seemed to realize her acceptance there with other children, and the parents reported that they observed a marked change in her feeling about herself (fig. 4).

Because the method of therapy was of an original nature and because of the encouraging results with this child, 5 other patients with anophthalmos were treated in a similar manner. The cases of 3 of these patients are reported.

A boy aged 9 months presented a clinically evident anophthalmos similar to that in the first case. A and B of figure 5 show this child after eight months of treatment, without the prosthesis in position. When treatment was begun, the patient had severe photophobia, and it was impossible to obtain adequate photographs. C and D of figure 5 show the child's appearance with the prosthesis in position.

These patients wear the prosthesis day and night and do not seem to be inconvenienced in any way. Tears flow over the face of the prosthesis, and because the posterior wall is in contact with the posterior wall of the cul-de-sac, any secretions accumulate in the inner and outer canthi of the palpebral fissure in a normal manner.

An infant or child with true anophthalmos presents the possibility of failure of facial growth without the ocular organ in position and without the opportunity for normal palpebral and ocular function.



Fig. 4.—The patient expresses her personal feeling of self assurance.

In figure 6 *A* and *B* is shown a woman aged 24 with a miniature cul-de-sac, infantile orbital features and anophthalmos clinically evident. This patient was treated in the same manner, with very evident changes in the cul-de-sac, as shown in figure 7 *A*, taken after nine months of treatment. Figure 7 *B* shows the changes in size of the prostheses that were worn, the first one being so small that it was necessary to use wax alone to obtain retention within the cul-de-sac. The patient was unusually enthusiastic about the results and gave cooperative home care between the intervals of treatment. The results shown in figure 6 *C* and *D* are notable, considering the period of time elapsed and the age of the patient.

Because it is reasonable to assume that, in still older patients, age might prevent the growth of the cul-de-sac, such a patient is shown in figure 8 *A* and *B*. This woman, who was past 40, had a miniature cul-de-sac and infantile features of the orbital area of the face. She



Fig. 5.—Infant boy aged 9 months at the time he was presented with a condition similar to that in the first case. (*A*) The prosthesis has been removed to illustrate the size of the palpebral fissure; (*B*) the profile shows necessity for maintaining the prosthesis in situ to preserve normal facial contour; (*C*) with the prosthesis in position the result of eight months of treatment is apparent, with the cul-de-sac approximately normal size; (*D*) profile with prosthesis in position shows restoration of the normal facial contours and stimulation of growth of the orbital area.

had never been able to wear a prosthesis of any type because the cul-de-sac was shallow and very small. A series of three prostheses



Fig. 6.—(A) A woman, aged 24, presented with a miniature cul-de-sac and failure in growth of the orbital area because of lack of correction. (B) Profile shows collapse of the lid cilia and depression in the orbital area of the facial contour. (C) Photograph nine months of treatment shows degree of restoration of the orbital area and increase in size of the palpebral fissure. (D) Profile shows increase in curvature of the lid cilia and degree of restoration to normal facial contour.



were made. The increased size of the cul-de-sac at the end of twelve months is shown in figure 8 *C* and *D*. The ptosis of the greater lid was overcome and the orbital area restored to more normal facial contours. It is hoped further to develop the orbital area by continued stimulation.

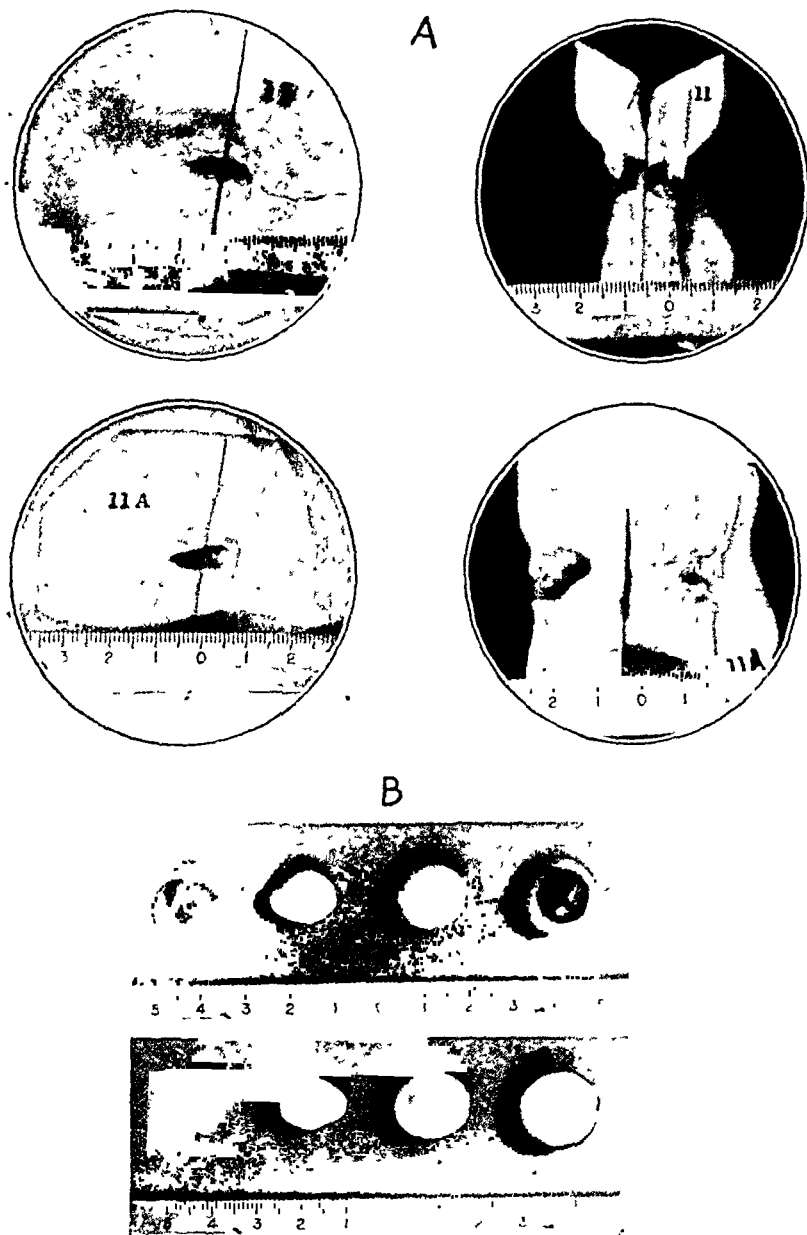


Fig. 7.—*A*: Upper circles: Cast made July 22, 1946: cul-de-sac approximately 8 mm. wide, 4 mm. deep and 6 mm. in vertical diameter. Lower circles: cast made April 14, 1947: cul-de-sac approximately 16 mm. wide, 15 mm. deep and 13 mm. in vertical diameter.

*B*: Upper figure: First prosthesis inserted was made of wax; then larger prostheses of scleral material were made until the iris could be inlaid into the sclera. Lower figure: Posterior views of the same prostheses show changes in the shape and size of the posterior wall of the cul-de-sac.

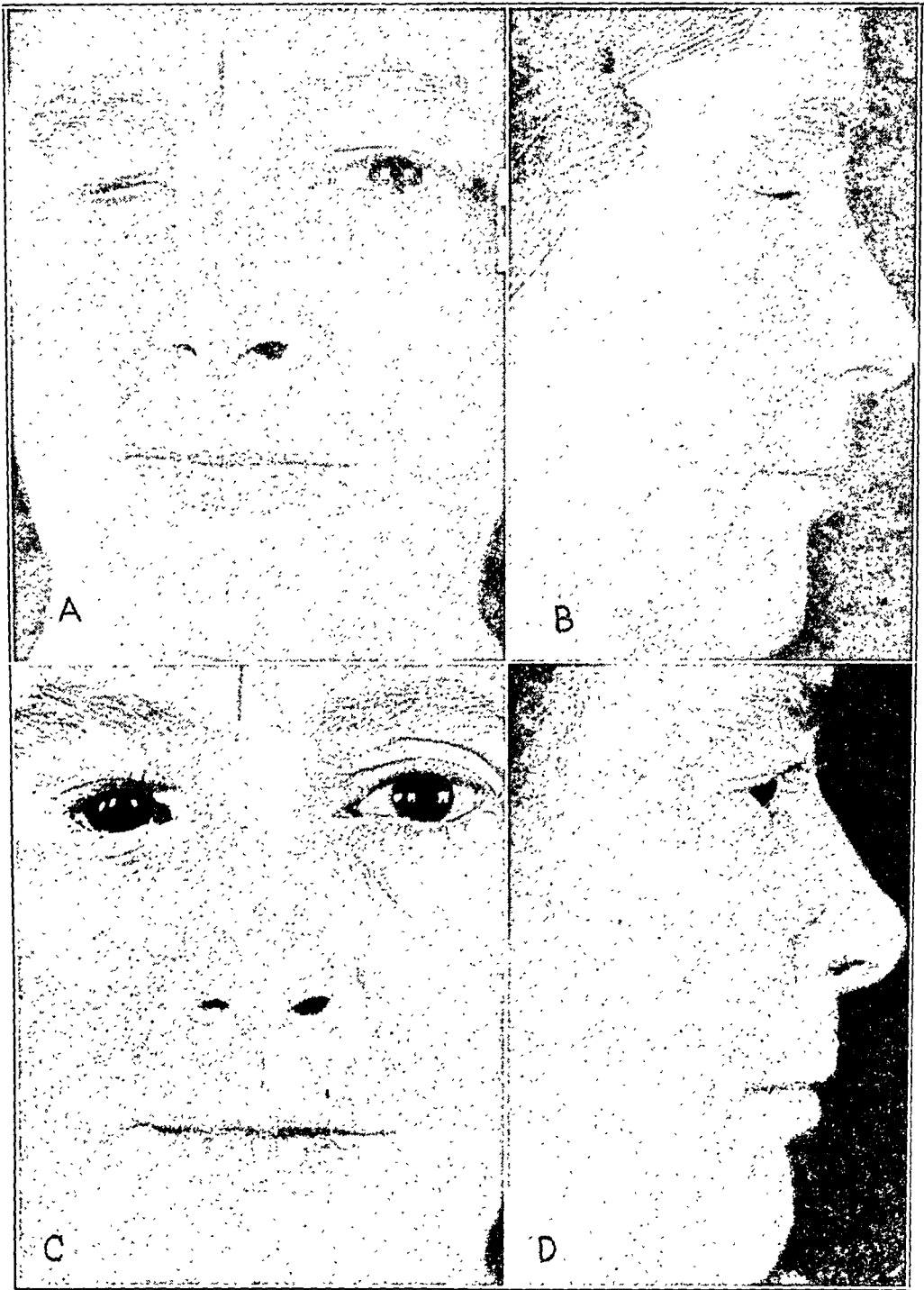


Fig. 8.—(A) Orbital area was infantile in development, due to lack of function since birth. (B) Profile view shows ptosis of the upper lid and marked endophthalmos. (C) The enophthalmos has been overcome considerably, and ptosis of the greater lid is improved. (D) Twelve months after treatment this prosthesis restores the orbital area to the extent shown.

## SUMMARY

The literature has not previously been concerned with esthetic correction of unilateral anophthalmos but, rather, has discussed the etiology.

The distinction between true anophthalmos and microphthalmos is of small clinical importance so long as the cul-de-sac presents no pathologic condition before construction of the prosthesis is begun.

Even though the report of previous cases of anophthalmos is rare, the presentation of this technic as a method of correction will result in many more cases being made available for correction.

The technic previously developed for loss of eyes due to war injuries is ideal for an approach to the problem of the miniature cul-de-sac associated with anophthalmos.

From the results obtained in the esthetic correction of anophthalmos by the ophthalmoprosthetic technic in the cases reported, it is evident that growth of the cul-de-sac and the orbital area of the face may be stimulated, in a manner similar to the growth of muscle and bone associated with facial changes produced by orthodontic correction.

Infants and children do not seem to experience any pain or discomfort during the period of construction and wear the prosthesis without being aware of its presence in the orbital socket.

Redundant tissue within the cul-de-sac is absorbed under the prosthesis; the muscular tone improves, and the conjunctiva and underlying tissues become smooth and a healthy pink while the patient is wearing the prosthesis. This occurs because the prosthesis fits all the tissues snugly and does not permit the accumulation of secretions behind it.

Unless an attempt at esthetic correction is made in infancy or early childhood, it is reasonable to assume that the orbital area of the face and the cul-de-sac will not develop in pace with the other facial features, a condition observed in the adults whose cases are reported in this paper. The psychologic effect observed during the period of growth stimulation of the orbital area and after the adequate prosthetic restoration of the eye is very noticeable, even in very young children. In figure 4, the expression on the child's face may be interpreted as one of increased self assurance. Parents and relatives living with such children after esthetic correction has been completed are enthusiastic and state that they observe a notable improvement in the child's social relations within the home and with other children during play periods and at school.

The present need for continued research in the field of ophthalmoprostheses and for further effort toward the esthetic correction of anophthalmos is of prime importance.

# NONPERFORATING THERMOMETRIC CYCLODIATHERMY IN TREATMENT OF HYPERTENSIVE UVEITIS

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AND

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IN 1942 we recommended the use of nonperforating cyclodiathermy in treatment of various forms of intraocular hypertension. Since then, we have endeavored to improve this operation and to determine its indications and the mechanism of its hypotensive effect.<sup>1</sup>

During this period, while all scientific exchanges between the United States and Belgium were cut off, Albaugh and Dunphy<sup>2</sup> described a similar operation. This, however, differs from ours in several points, which we shall comment on later.

## NONPERFORATING THERMOMETRIC CYCLODIATHERMY

*Diathermy Apparatus.*—A diathermy electrode is applied to the eyeball at the posterior edge of the ciliary body, and the heating of the tissues (fig. 1) is effected with the high frequency current.

The apparatus has two circuits: One, the diathermy circuit, generates the high frequency current and produces the heating of the tissues; the other, the thermometer circuit, provides for the measurement of the tissue temperature.

It is not necessary to describe the diathermy circuit, as it has no special features. We use a bipolar current. The passive electrode is placed on the patient's back. The active electrode, placed on the eyeball, is made of a copper cylinder, 0.6 or 0.8 by 1 mm.

The thermometer circuit is made according to Coppez's<sup>3</sup> diagram (fig. 2). It includes a cold thermoelectric couple, immersed in ice, and a hot thermoelectric couple, placed on the eyeball at the same place as the active diathermy electrode. The manufacture of small thermoelectric couples presents difficulties. We shall briefly describe the hot couple.

It is made of two wires—one of copper, the other of constantan. The diameter of the copper wire is 0.6 or 0.8 mm. This is the active electrode described in the

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From the Ophthalmologic Clinic, University of Liège, Hospital of Bavière.

1. Weekers, L., and Weekers, R.: *Ophthalmologica* **104**:1, 1942; **109**:218, 1945; *Acta ophth.* **24**:1, 1946; *Ann. d'ocul.* **180**:10, 1947; *Bull. Soc. belge d'opht.* **81**:50, 1945; **85**:38, 1946.

2. Albaugh, C. H., and Dunphy, E. B.: *Cyclodiathermy: Operation for Treatment of Glaucoma*, *Arch. Ophth.* **27**:543 (March) 1942.

3. Coppez, L.: (a) *Ophthalmologica* **109**:80, 1945; (b) *Bull. et mém. Soc. franç. d'opht.* **59**:237, 1946.

diathermy circuit. It therefore belongs both to the thermometer and to the diathermy circuit. The diameter of the constantan wire is 0.1 mm. It belongs to the thermometer circuit only. These two wires are welded to form the thermoelectric couple. This welding was carried out in two ways, and both were satis-

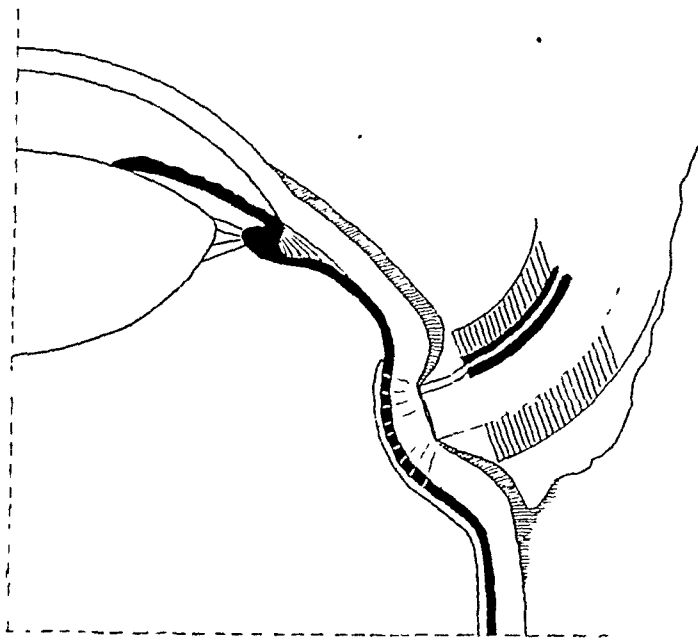


Fig. 1.—Scheme showing the place of application of the thermometric electrode, on the posterior edge of the ciliary body, 8 mm. from the limbus.

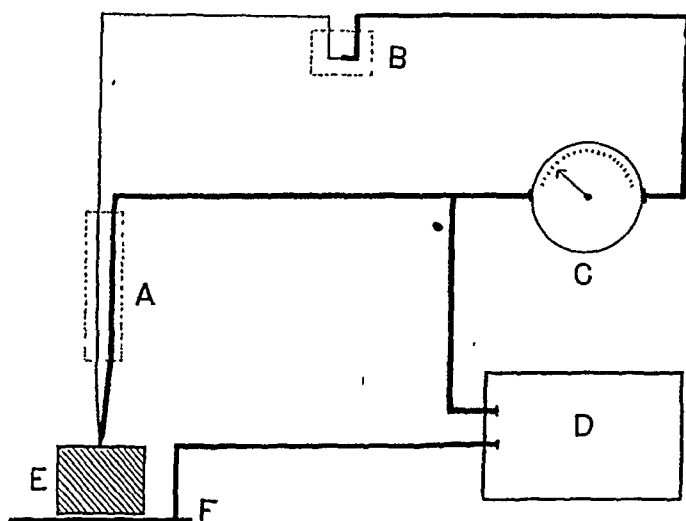


Fig. 2.—Scheme of the diathermic and thermometric circuits (from Coppez<sup>3b</sup>). *A* indicates hot thermoelectric couple (active electrode); *B*, cold thermoelectric couple (immersed in ice); *C*, millivoltmeter, used as a thermometer; *D*, diathermy apparatus; *E*, patient; *F*, passive electrode.

factory (fig. 3). When the two couples of the thermoelectric circuit have different temperatures, there is a difference of potential between them. The latter is proportional to the difference of temperature. It is measured by the millivoltmeter placed

in the circuit. The latter is graduated empirically in degrees centigrade and serves as a thermometer.

*Technic of the Operation.*—The anesthesia of the eyeball is obtained by instillations of cocaine and epinephrine and by a retrobulbar injection of 2 cc. of 4 per cent

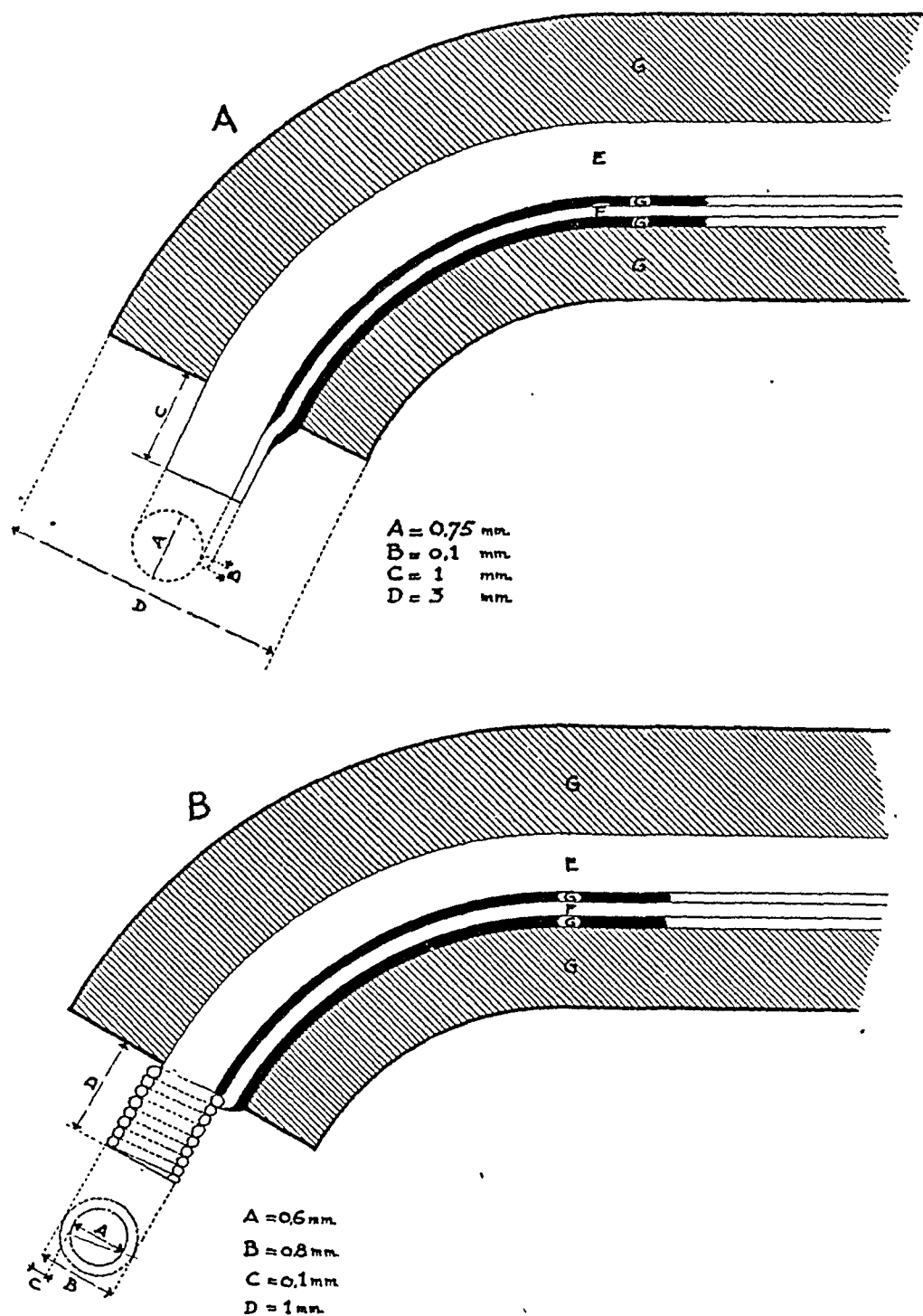


Fig. 3.—Thermometric electrodes.

In both diagrams, E indicates the copper wire; F, the constantan wire, and G, the insulation.

procaine hydrochloride. If sufficient time elapses (ten minutes at least), this anesthesia renders the operation painless.

The lids are held open with a blepharostat. The electrode is placed directly on the eyeball, without dissection of the conjunctiva. The use of forceps is not necessary. The pressure of the electrode fixes the eyeball.

The place where the electrode is applied should be carefully chosen. The effects on tension and the risk of complications are greater the nearer this site is to the limbus. The electrode must be placed, at the ora serrata, at the back of the ciliary body, 8 mm. from the limbus (fig. 1). The number of applications varies from twelve to twenty (fig. 4). Twelve to sixteen applications are, as a rule, sufficient to normalize the ocular pressure permanently in cases of hypertensive uveitis. When the electrode is applied twelve times, the coagulated areas in the conjunctiva are separated by a band of apparently normal tissue. When the electrode is applied twenty times, the coagulated areas touch one another. It is the same with the areas of postoperative chorioretinitis, as shown by the ophthalmoscope; these will be described later. Each application lasts fifteen seconds.

The temperature shown by the millivoltmeter used as a thermometer at the moment of the application of the electrode is that of the conjunctiva, i. e., approxi-

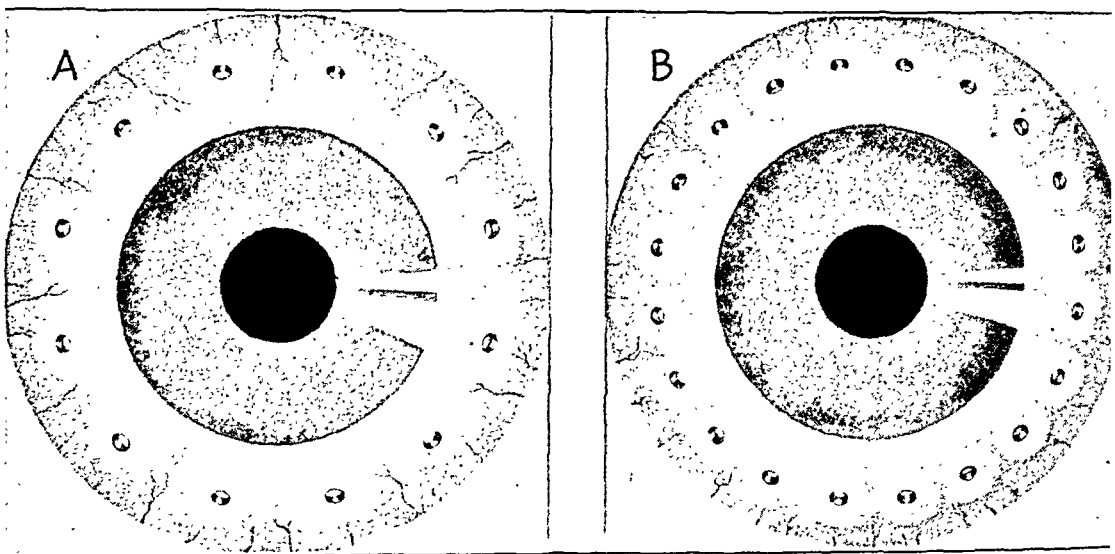


Fig. 4.—Diathermic coagulation made 8 mm. from the limbus. *A*, twelve coagulations; *B*, twenty coagulations.

mately 30 C. The rheostat is adjusted in such a way that the temperature rises rapidly when the current is turned on. We try to reach 90 C. at the fifth second. This temperature must be maintained as constant as possible for ten seconds (fig. 5). At the fifteenth second, the current is turned off and the electrode is removed. It is necessary, in order to avoid desiccation of the cornea and to prevent a lesion, to close the eyelids for a few moments after three or four consecutive applications.

After the operation, penicillin ointment and a dressing are applied three times a day for forty-eight hours. After that, it is sufficient to wash the eye two or three times a day with a solution of tepid isotonic sodium chloride solution U. S. P. as long as the postoperative reaction lasts, that is, for two or three weeks. In case of hypertensive uveitis, we carry on the treatment with atropine when necessary.

*Observations.*—After the operation, when the pupil is wide, the chorioretinal lesions caused by the diathermy burn can be observed with

the ophthalmoscope. For six to seven days, the ophthalmoscopic image consists of a ring of retinal edema. Each patch of edema is circular, slightly raised, 3 or 4 papillary diameters in width and close to the next patch. The edema is white, with a few hemorrhages; the retinal vessels are bent when passing from the normal to the edematous retina (fig. 6 *A*). Ten days after the operation, the edema is less, and the patches are smaller and less prominent. Brownish, irregularly distributed pigmentary spots appear in the retina, and the hemorrhages are less visible (fig. 6 *B*).

Twenty to thirty days after the operation, the patches have a new aspect and the chorioretinal scars are now formed; they are flat, circular, with sharp edges; the diameter is less than 3 papillary diameters, and the retina and choroid are atrophic. A few vessels of the retina and choroid remain, clearly visible against the white background of the

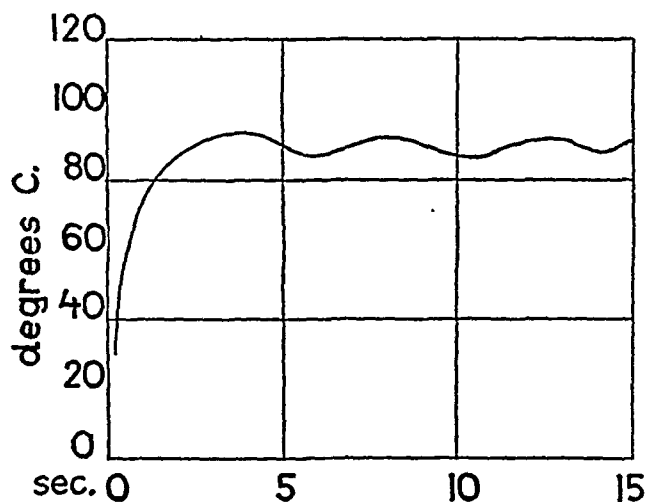


Fig. 5.—Increase in the tissue temperature produced by the diathermic current.

sclera. There are dense pigmented spots, with irregular edges. The chorioretinal patches along the ora serrata are somewhat similar to the postoperative scars after retinal dialysis (fig. 6 *C*).

The successive improvements in the technic of nonperforating cyclo-diathermy have made it an easy and well controlled operation, the effects of which can be graduated at will. When correctly performed, it is quite without danger. Its hypotensive effect is considerable and lasts according to the degree of the intraocular hypertension. Its indications have become precise. In addition to the hypertensive uveitis studied in this paper, nonperforating cyclodiathermy should also be used in treatment of (*a*) hypertension persisting after a filtering operation; (*b*) absolute glaucoma, especially when the eyes are painful, and (*c*) intraocular hypertension following corneal transplantation.

The operation described by Albaugh and Dunphy<sup>2</sup> presents features which are similar to ours, namely, the use of a nonperforating, flat



electrode, and the application of this electrode to the posterior extremity of the ciliary body. It differs from our operation, however, in three points. 1. Albaugh and Dunphy perform a dissection of the conjunctiva, which we do not regard as necessary. 2. They operate on one-half the circumference of the ciliary body. Previous experimental researches have demonstrated that when the operation is performed in a small territory it becomes necessary to use a more intense diathermy current to obtain a sufficient effect on the ocular pressure (Weekers and Weekers<sup>1</sup>). 3. They do not use a thermometer electrode, which enables us to regulate our intervention and to repeat it under identical conditions.

Thermometric nonperforating cyclodiathermy, carried out in the way we have described, does not lead to postoperative complications. From this point of view, it is quite different from Vogt's perforating

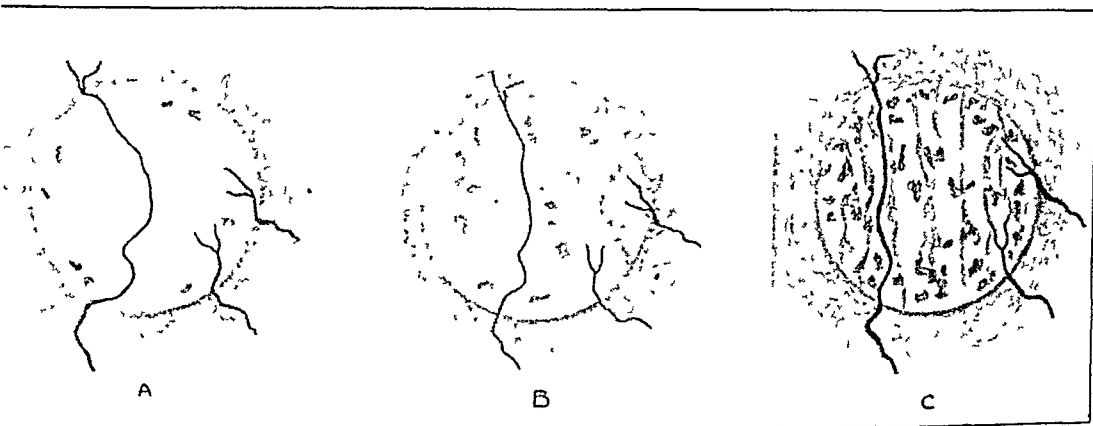


Fig. 6.—Ophthalmoscopic images of the diathermic coagulation at the ora serrata. *A* (twenty-four hours after operation): white, salient edema 4 papillary diameters wide; a few small blood suffusions. *B* (ten days after operation): The edema allows the retinal pigment to show through. *C* (thirty days after operation): Atrophy of the retina and choroid and persistence of the vessels; irregular distribution of the retina and choroid pigments. The sclera is visible.

cyclodiathermy (*Diathermiestichelung*), the complications of which are known (corneal ulcer, iritis, cataract and sympathetic ophthalmitis). Sugar<sup>4</sup> observed that Vogt's cyclodiathermy leads to synechias in the iridocorneal angle. Gonioscopic observations, now in progress, demonstrate that such is not the case after nonperforating thermometric cyclodiathermy. In the case of iritis, this operation does not even stimulate the formation of preexisting synechias in the angle of the iris.

*Results of Treatment of Hypertensive Uveitis with Nonperforating Thermometric Cyclodiathermy.*—Treatment of ocular hypertension complicating various forms of iridocyclitis and uveitis is a difficult problem.

4. Sugar, H. S.: Gonioscopy and Glaucoma, *Arch. Ophth.* 25:674 (April) 1941.

Miotics (pilocarpine, physostigmine and dis-isopropyl fluorophosphate [DFP]) are contraindicated; they increase the ocular congestion, facilitate the appearance of synechias and jeopardize the future of the eye and its functions.

Mydriatics, on the other hand, have a favorable influence on the uveitis and, consequently, on the intraocular hypertension. The instillation of drops of atropine (1 per cent) in an eye with hypertensive uveitis is without danger. We often use it, and the results are most favorable. The instillation of drops of epinephrine hydrochloride, 2 per cent, is useful to break down recent synechias in cases of the acute form (Weekers, Joiris and Bonhomme<sup>5</sup>).

When the mydriatic treatment is insufficient to decrease the tension, we practice a retrobulbar injection of alcohol (1.5 cc. of 40 per cent alcohol); this reduces the ocular pressure and has a favorable action on the iridocyclitis (Weekers,<sup>6</sup> Magitot and Morax<sup>7</sup>).

An eye with iridocyclitis can often bear a moderate increase of tension for a long period without any visual decrease.<sup>8</sup> Later, temporizing becomes dangerous, and the operation can no longer be postponed. In such cases, we used to practice iridencleisis ab externo, as described by L. Weekers in 1936.<sup>9</sup> The results were satisfactory. They have recently been confirmed by Kalt.<sup>10</sup> This author operated in 22 cases of hypertensive iridocyclitis. The ocular tension was definitely normalized in 86 per cent and the visual acuity was improved in 60 per cent of the cases.

We now prefer nonperforating cyclodiathermy in the treatment of hypertensive uveitis. This new operation has been performed on 12 patients with uveitis complicated by ocular hypertension, including 10 patients with uveitis of tuberculous origin, 1 patient with diabetic uveitis and 1 patient with Besnier-Boeck-Schaumann disease (generalized sarcoidosis).<sup>11</sup> In other words, all the patients had chronic, malignant types of uveitis, complicated by a definite and dangerous rise in ocular pressure.

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5. Weekers, L.; Joiris, P., and Bonhomme, F.: *Arch. d'opht.* **3**:97, 1939.

6. Weekers, L.: *Ann. d'ocul.* **176**:81, 1939.

7. Magitot, A., and Morax, P.: *Bull. Soc. d'opht. de Paris* **49**:617, 1937.

8. The visual functions must be tested with the most sensitive methods: angioscotometry; campimetry in weakened light; perimetry with luminous spots of low brilliance, and measurement of fusion frequency and of dark adaptation.

9. Weekers, L.: *Arch. d'opht.* **53**:166, 1936.

10. Kalt, M.: *Bull. et mèm. Soc. franç. d'opht.* **59**:230, 1946.

11. Recently, we have treated several more patients, among whom were one with Fuchs's heterochromia and one with syphilitic uveitis, both complicated by hypertension. The immediate results were favorable, and the patients are being kept under observation for further study.

The results are presented diagrammatically (fig. 7). The initial tensions, before the cyclodiathermy, vary from 30 to 50 mm. of mercury. The intervention in most cases produces a rapid and considerable fall of the ocular pressure. Fifteen days after the cyclodiathermy, the ocular pressure is in the majority of cases lower than 23 mm. of mercury. The hypotensive effect of cyclodiathermy lasts a long time and is generally sufficient to neutralize the phase of hypertension due to the uveitis. In 1 case (Besnier-Boeck-Schaumann disease) a relapse of the uveitis, complicated by further hypertension, compelled us to repeat the operation three months later. This was followed by an immediate and lasting fall in tension. These results are satisfactory, considering the serious nature of the uveitis and the usual

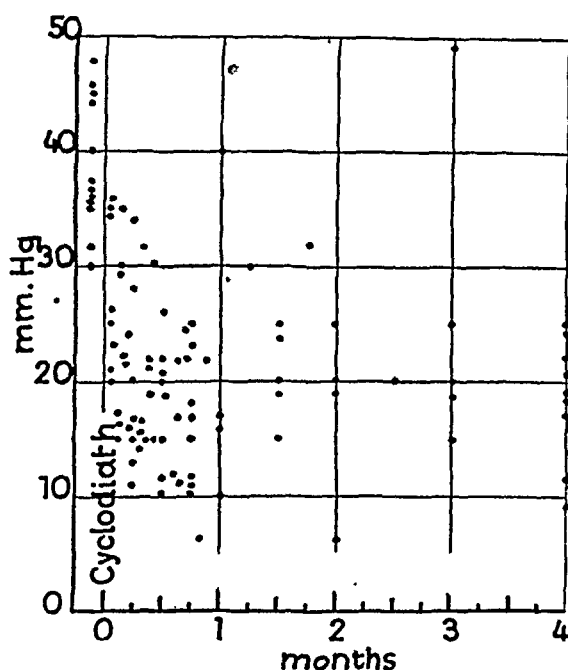


Fig. 7.—Hypotensive effects of thermometric nonperforating cyclodiathermy in 12 cases of hypertensive uveitis.

malignancy of the resulting hypertension. We now apply cyclodiathermy very early, without even carrying out the preliminary retrobulbar injection of alcohol.

When there is pupillary seclusion, cyclodiathermy is contraindicated. It is necessary in such cases to reestablish the passage of the aqueous humor through the diaphragm of the iris. Iridencleisis is indicated in these cases. The only object of cyclodiathermy is to relieve ocular hypertension; the local treatment with mydriatics and the general treatment should not be interrupted.

It is difficult to judge the influence of cyclodiathermy on the inflammatory process. The anatomic changes are often serious at the time

of intervention (synechias, cloudiness of ocular media, cataract). Sometimes one has the impression that, apart from its hypotensive effect, cyclodiathermy influences favorably the inflammatory process of the uveitis. One thing is certain: It removes the immediate and serious threat of hypertension.

#### CONCLUSIONS

Thermometric nonperforating cyclodiathermy should be used in treatment in certain cases of ocular hypertension. Its main advantages are as follows: (*a*) It is easy to perform; (*b*) opening of the sclera is avoided; (*c*) the operation can be regulated at will; (*d*) it does not lead to any complications.

The hypotensive effect of nonperforating diathermy is definite and lasting in accordance with the nature of the glaucomatous process. It is less than that of iridencleisis and is of shorter duration.

The main indications for thermometric nonperforating cyclodiathermy are as follows: (*a*) uveitis complicated by intraocular hypertension; (*b*) hypertension persisting after a filtering operation; (*c*) painful, absolute glaucoma, and (*d*) intraocular hypertension after corneal transplantation.

Hospital of Bavière.

## LYMPHOSARCOMA OF THE EYELID

Report of Case, With Death in Forty Days

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LESS THAN 1 per cent of all lymphosarcomas originate in the region of the eye. When it does arise in the lid or the orbit, lymphosarcoma, although it infiltrates to a limited extent, tends to be a well circumscribed and slow-growing tumor; the other tissues of the body are not usually involved for many months or years. Lymphosarcoma also appears microscopically benign, with relatively well differentiated cells and few mitoses. Surgical removal may be followed by survival for many years, and irradiation has proved efficacious in ameliorating the disease for considerable periods. Cases of lymphosarcoma of the eyelid and/or orbit have recently been reported by Metivier,<sup>1</sup> Cookson and MacRae,<sup>2</sup> Michail,<sup>3</sup> Tooke,<sup>4</sup> Wheeler,<sup>5</sup> Jensen,<sup>6</sup> Siatto,<sup>7</sup> Hine,<sup>8</sup> Perera,<sup>9</sup> Black<sup>10</sup> and Rados.<sup>11</sup>

From the Institute of Ophthalmology of the Presbyterian Hospital in the City of New York.

1. Metivier, V. M.: Lymphosarcoma of Eyelid, *Brit. J. Ophth.* **21**:202-206, 1937.

2. Cookson, H. A., and MacRae, A.: Lymphoid Tumor of the Lacrymal Gland, *Brit. J. Ophth.* **22**:385-391, 1938.

3. Michail, D.: Sur les lymphomes symetriques des glandes lacrymale, *Ann. d'ocul.* **175**:565-581, 1938.

4. Tooke, F. T.: A Case of Aleukemic Lymphosis Involving the Upper Lids, with Pathologic Findings, *Tr. Am. Ophth. Soc.* **36**:268-276, 1938; *Brit. J. Ophth.* **23**:444-454, 1939.

5. Wheeler, M. C.: Malignant Neoplasm of the Eyelid: Report of Two Cases, *Arch. Ophth.* **20**:682 (Oct.) 1938.

6. Jensen, J. P.: Conjunctival Lymphoma, *Acta ophth.* **18**:67-75, 1940.

7. Siatto, G.: Contributo alla conoscenza del reticuloma della congiuntiva: Osservazione clinico-istologica, *Rassegna ital. d'ottal.* **9**:477-486, 1940.

8. Hine, M. L.: Report of a Case of Lymphoma of the Orbit, *Brit. J. Ophth.* **26**:297-301, 1942.

9. Perera, C. A.: Lymphosarcoma of the Lacrymal Gland: Report of a Case with Giant Lymph Follicle Hyperplasia, *Arch. Ophth.* **28**:522-529 (Sept.) 1942.

10. Black, G.: Reticulum Cell Sarcoma, *Tr. Ophth. Soc. U. Kingdom* **62**:316-319, 1943.

11. Rados, A.: Reticulum Cell Sarcoma of the Conjunctiva, *Arch. Ophth.* **35**:400-414 (Jan.) 1946.

More commonly, lymphosarcoma begins in the cervical, axillary, mediastinal or mesenteric lymph nodes, or in the lymphoid tissue of the nasopharynx, stomach or intestine. It is generally a malignant tumor, expanding in a frankly invasive and destructive manner, sometimes like an ordinary neoplasm, with a focal origin and spread by infiltration and metastasis; but often it shows its relationship to the leukemias and to Hodgkin's disease by an apparently pluricentric origin, occurring simultaneously or successively. Secondary invasion usually involves other lymph nodes, both near and distant, to be followed by the infiltration of other organs containing lymphoid tissue, such as the liver, lungs and kidneys. Pathologically, the predominant cell may be any one of the lymphoid series, thus giving rise to the lymphocytic cell type, the reticulum cell type and the giant follicle cell lymphosarcoma. The cell type may change during the course of the disease, or different cell types may be found in different locations in the same patient. Clinically, in addition to the symptoms referable to the tumor, there may be anemia, due to depression of red blood cell formation, and a moderate leukocytosis is seen in about half the cases. Lymphosarcoma must be distinguished<sup>12</sup> from other metastatic tumors of the lymphatic system, such as lymphatic leukemia, Hodgkin's disease, chloroma, pseudoleukemia, mycosis fungoides, Mikulicz' syndrome and, most important of all, benign hyperplasia of lymphatic tissue. It is probable that many of these conditions are closely related and differ only in the character of the proliferative activity. In the majority of cases, the tumors in the region of the eye are probably part of a systemic disease that will sooner or later involve a great portion of the lymphoid tissue of the body.

The present case is reported, not because it represents a rare tumor, but for its unusual features. Clinically, the case was unusual in that (1) the lesion was considered an atypical, low grade inflammatory process by all who examined the patient, and (2) the disease progressed

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12. The differentiation of these related conditions is one of the complex problems of pathology; for a discussion of this subject, attention is invited to the following publications: (a) Callender, G. R.: Tumors and Tumor-Like Conditions of the Lymphocyte, the Myelocyte, the Erythrocyte, and the Reticulum Cell, *Am. J. Path.* **10**:443-466, 1934. (b) Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1940, pp. 396-433. (c) Krumbhaar, E. B.: The Lymphomatoid Diseases: So-Called Lymphoblastomas, *J. A. M. A.* **106**: 286-291 (Jan. 25) 1936. (d) Kundrat, L.: Ueber Lympho-Sarkomatosis, *Wien. klin. Wchnschr.* **6**:211 and 234, 1893. (e) Minot, G., and Isaacs, R.: Lymphoblastoma and Malignant Lymphoma, *J. A. M. A.* **86**:1185-1189 (April 17) 1926. (f) Robb-Smith, A. H. T.: Reticulosis and Reticulo-Sarcoma: A Histological Classification, *J. Path. & Bact.* **47**:457-480, 1938. (g) Stout, A. P.: *Human Cancer*, Philadelphia, Lea & Febiger, 1932, pp. 795-838.

rapidly to a fatal termination in forty days. Pathologically, the neoplasm in this case is unique because of (1) the meager amount of involvement of the lymph nodes and (2) the rapid, destructive spread to involve all the viscera and other tissues of the body.

#### REPORT OF CASE

Mr. B. J. B., a Jewish machinist aged 49, consulted his family physician on May 9, 1947, with the complaint that a hot chip of metal had flown into his right eye two days previously. The piece of steel had been removed immediately in the shop, but the following day the eye was red, with a purulent discharge. His physician made a diagnosis of acute purulent conjunctivitis and prescribed sulfathiazole ophthalmic ointment. On May 14 there developed an inflammation of the right lower lid near the inner canthus, which subsided with treatment. Two weeks later the lids of the right eye began to swell. He went to see his physician again on June 2, and hospitalization for the administration of penicillin was advised. After two days of this regimen sulfadiazine was combined with the penicillin, and on June 9 they were both discontinued and streptomycin treatment was instituted. Two days later penicillin was given again, this time in combination with streptomycin.

An ophthalmologist was then asked to see the patient, and the diagnosis of orbital cellulitis and abscess of the right lower lid was made. Incision into the apparent abscess was performed but no discharge was obtained. Roentgenograms of the orbit and sinuses revealed no abnormality. Examination of the blood showed a white cell count of 15,450, with 78 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. Cultures of material from the conjunctival sac yielded only diphtheroids and *Staphylococcus albus*. There was no pain or discomfort and no fever. On June 18 the antibiotics were discontinued because it was thought they were masking the picture. At this time the swelling of the lids had progressed so that the patient was unable to open his eye. In the last examination of the globe itself, on that date, the media and fundus appeared normal. The patient was then referred to the Institute of Ophthalmology of the Presbyterian Hospital, to the service of Dr. Algermon B. Reese, for further study.

The patient was admitted to the Institute of Ophthalmology on June 24; at this time he presented a hard, red swelling of the right eyelids and the right side of the face, including the submaxillary region. The right eye was not examined because the lids could not be everted or retracted. No lymphadenopathy was found, but there appeared to be an abscess in the submaxillary region. General physical examination disclosed nothing abnormal. The patient had never had any serious illness; he had had a submucous resection at the age of 12.

The impression at the time of admission was that of a fungous infection of the right orbit and the right side of the face. Figure 1 is a photograph of the patient at the time of admission to the Institute. On the day following admission, an incision was made in the medial half of the right lower lid and carried back into the orbit; the floor of the orbit was explored to the apex, but no pus or exudate was obtained. Cultures for bacteriologic examination were taken at various depths of the incision, but subsequent investigation of these cultures revealed only a few, nonpathogenic, bacteria. Cultures of tears and of material from the conjunctiva, lid margins and skin of the face disclosed nothing more than

the normal flora. Blood cultures were sterile. Roentgenograms of the heart and lungs were observed to be well within the limits of normal variation. Stereoscopic roentgenograms of the skull were reported to show some necrotic teeth, increased density of the soft tissue of the right orbit, massive swelling of the soft tissues of the right side of the face, clouding of the right ethmoid labyrinth, thickening of the lining membrane of the right antrum and clear sinuses on the left side. The blood count at this time was as follows: red cells, 4,120,000; hemoglobin, 90 per cent, or 13.1 Gm. per hundred cubic centimeters; white cells, 17,000, with 73 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 4 per cent monocytes, 2 per cent eosinophils, 1 per cent basophils and 5 per cent band forms. All other laboratory procedures were noninformative.



Fig. 1.—Photograph of the patient at the time of his admission to the hospital.

During the first week in the hospital, the mass increased greatly in size, extending down over the angle of the jaw to involve the whole right side of the neck. The nose was displaced farther to the left, and the right ear was pressed posteriorly. It became difficult for the patient to open and close his jaws; there was no pain, but only mechanical discomfort. The right eyelids were solidly closed. The surgical incision in the right lower lid did not heal. The mass in the neck did not resemble typical cervical adenopathy but appeared to be a subcutaneous inflammatory swelling, continuous with that of the face. At this time, a few small nodes became palpable in the right axilla, and the liver was found to be 2 fingerbreadths below the costal margin. On June 30 a biopsy



was performed on the mass over the angle of the jaw; microscopic examination of the sections disclosed a highly malignant lymphosarcoma of the reticulum cell type.

In the second week of his hospitalization, the patient's general condition deteriorated rapidly; he became silent, morose and depressed. He ate little, and eating was followed by nausea and vomiting. His fluid intake and output decreased markedly. With evidence of widespread dissemination of the disease nitrogen mustard (tris-[2-chloroethyl] amine hydrochloride) therapy was favored initially, rather than irradiation. A course of nitrogen mustard (12 mg. daily) was given on July 4, 5 and 6. On the following day there was a striking decrease in the size of the tumor of the face and neck, and the cervical mass was scarcely palpable. The swelling was reduced to such an extent that the lids were easily opened and



Fig. 2—Photograph of the patient one day after completion of the course of nitrogen mustard (one day before his death).

the eye could be examined; no pathologic process was found. Figure 2 is a photograph taken on July 7. The patient suffered increasing nausea and vomiting; infusions of dextrose solution were given. The blood count now showed 4,190,000 red cells, 78 per cent hemoglobin and 2,900 white cells, with 58 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes, 8 per cent monocytes and 14 per cent band forms.

On the morning of July 8 the patient evidenced definite, acute cardiac distress; this was the first time that cardiac symptoms had been noted. The nurse found him too weak and unsteady to go to the bathroom; while using the bedpan, he shouted for help, and the nurse found him unconscious. A few moments later a member of the house staff pronounced him dead, evidently from respiratory arrest.

## PATHOLOGIC EXAMINATION

*Biopsy of Specimen from Jaw* (June 30).—The biopsy specimen yielded sections showing skin and subcutaneous tissue on one aspect. Microscopically, the subcutaneous tissue was entirely replaced by a broad sheet of large, pale cells with ovoid or rounded nuclei, among which one could easily see many mitoses. The cells showed no tendency toward any grouping or structure; they were simply packed closely together. They contained moderate amounts of pale cytoplasm; there were granules of chromatin in the nuclei, lending a reticulated appearance. The uniformity of the cellular morphology was striking. No reticular network could be made out in these sections; the normal subcutaneous tissue was entirely

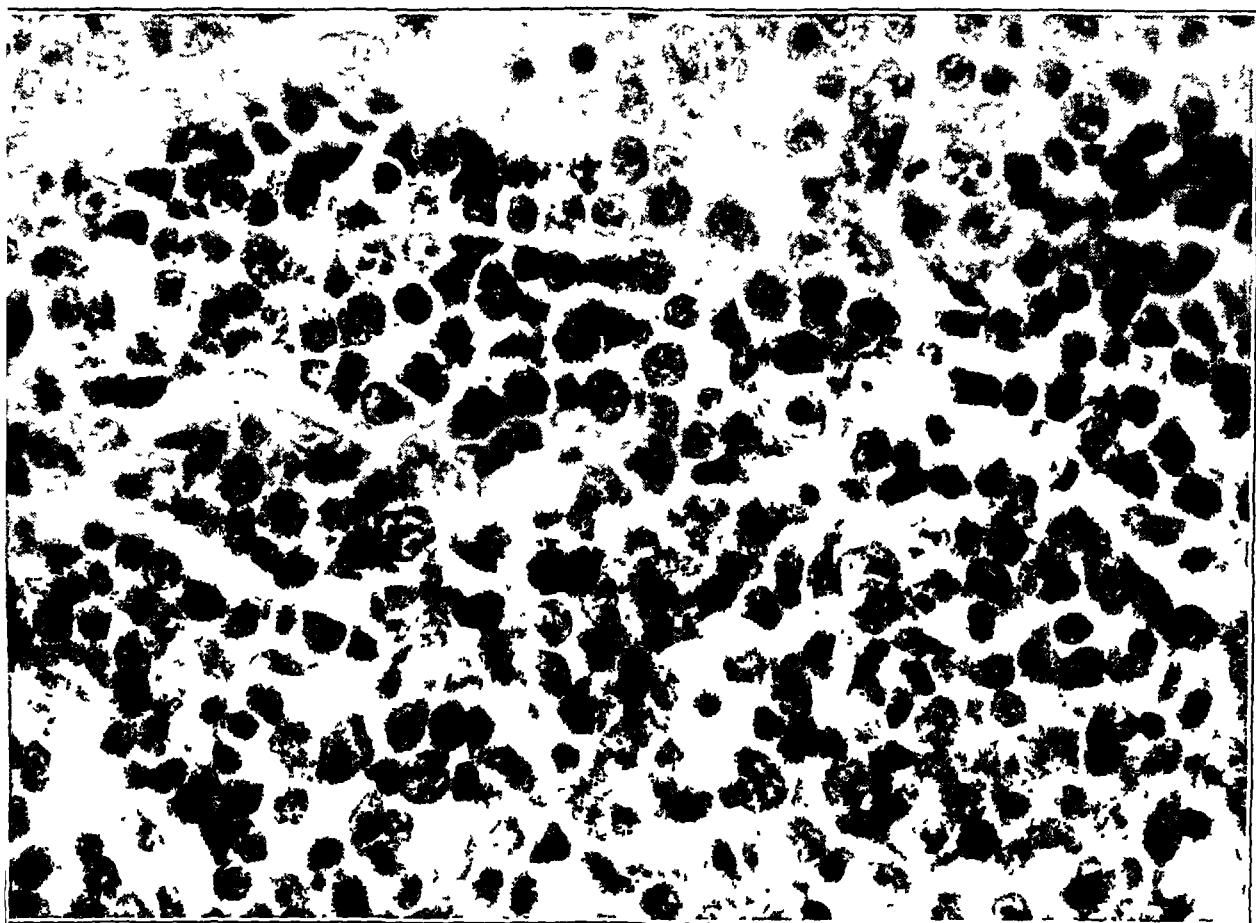


Fig. 3.—Photomicrograph of a section from the biopsy specimen from the jaw.

obliterated. The tumor cells were at least twice as large as a lymphocyte; therefore, this tumor was considered a reticulum cell type of lymphosarcoma. The histologic picture was similar to that of metastatic carcinoma in a lymph node but for the lack of any tendency to glandular or epithelial structure. Figure 3 is a photomicrograph from a section of the biopsy specimen.

*Postmortem Examination.*—*Macroscopic Observations:* The body was that of a well developed and well nourished white man of middle age. Externally, one saw the closed right eye and the tumor of the right side of the face and neck. Matted lymph nodes could be palpated in the right cervical and submaxillary areas; a few discrete nodes were present in the right axilla. Internally, the musculature

of the right ventricle of the heart exhibited a peculiar gray color; otherwise the thoracic cavity appeared normal. The liver could be palpated 2 fingerbreadths below the right costal margin; on section through the parenchyma, a small hemangioma, about 7 cm. in diameter, was disclosed. The external surface of the kidneys exhibited many light gray areas, from 1 to 2 cm. in diameter, which were not raised above the renal surface; on section, these gray lesions were seen to extend into the renal cortex. The intestine showed scattered, patchy, black lesions throughout the mucosal surface; there was no evidence of ulceration or bleeding into the lumen. The lymph nodes of the mesentery were enlarged and appeared yellow on cut surface.

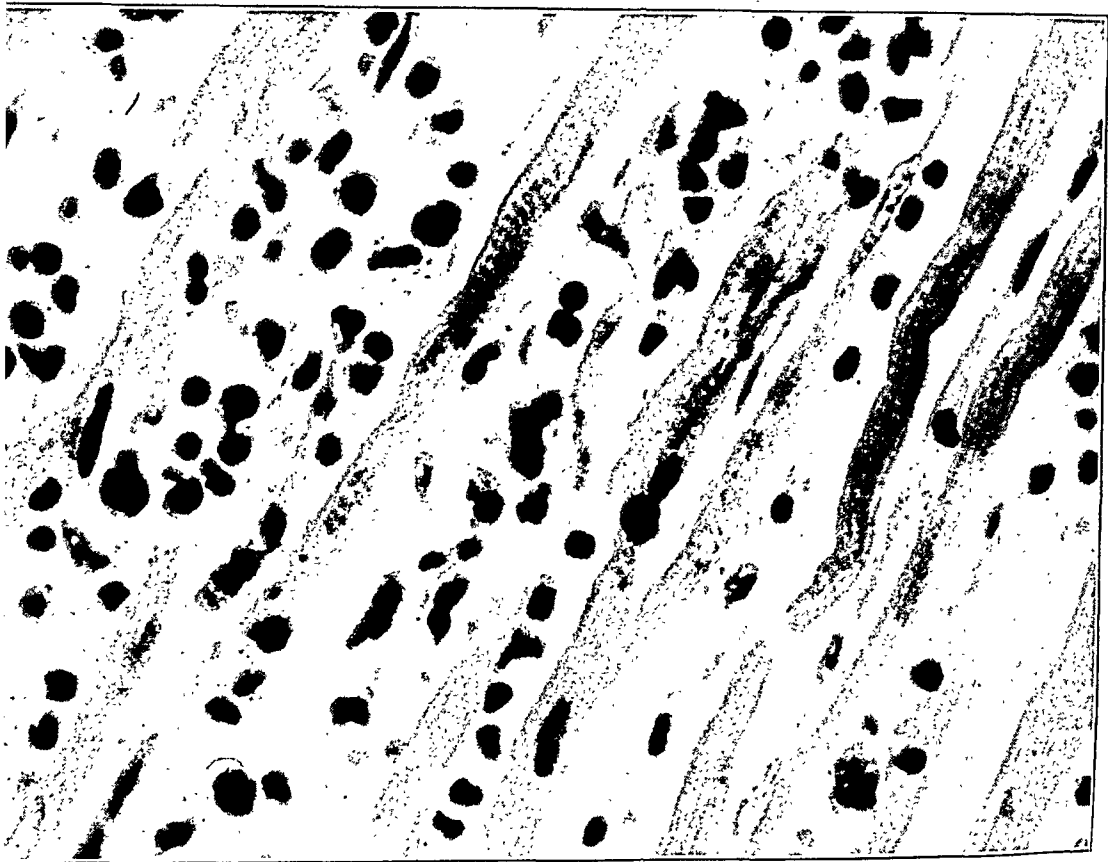


Fig. 4.—Photomicrograph of a section from the right ventricle, showing the wide separation of the cardiac muscle fibers by the tumor cells.

**Microscopic Observations:** Microscopically, extensive infiltration of the tumor cells was observed in the heart, liver, kidneys, spleen, stomach, pancreas and intestine.

**Heart:** The myocardium of the right ventricle showed an extensive, diffuse infiltration of hyperchromatic cells (closely resembling lymphocytes) with round nuclei and a slight amount of basophilic cytoplasm; again, the uniformity of these cells was striking. The muscle fibers, which appeared very thin and scanty, were widely separated by the accumulations of these cells. Figure 4 is a photomicrograph of a section from the right ventricle. It was amazing that the right ventricle was so largely replaced by tumor tissue and yet the patient showed no evidence

of cardiac failure until the day of his death. The left ventricle did not exhibit this extensive invasion; only small deposits of the tumor cells were seen under the epicardium. Moderate arteriosclerotic changes in the aorta and slight intimal thickening of the coronary vessels were the only other cardiac lesions noted.

Lungs: There were several small areas of infiltration of tumor cells about the arteries. The alveoli and most of the interstitial tissue showed no infiltration and appeared normal.

Liver: Localized groups of the same kind of tumor cells were present about the portal radicles. The section taken from the hemangioma showed endothelium-lined spaces containing erythrocytes; the fibrous septums dividing these sinusoids contained collections of the small dark tumor cells. The hepatic architecture was generally normal; a few lobules of fat could be seen in the hepatic cells about the central vein.

Spleen: The malpighian corpuscles stood out on cut section in the usual manner; the predominant cell was the small, dark-staining type described in the myocardium. The only unusual feature about the lymphoid tissue was the concentration and uniformity of this cell type. The red pulp and the capsule appeared normal.

Pancreas: Localized collections of small, dark lymphocytes could be seen in the connective tissue about some of the pancreatic ducts. The general architecture and the composition of the glandular tissue appeared normal.

Adrenal glands: The appearance was not unusual.

Kidneys: The renal cortex had been extensively and diffusely invaded by the tumor cells; they were the same lymphocytoid cells, with dark, round nuclei and scanty cytoplasm. The infiltration of the cortex appeared recent, inasmuch as there was little or no distortion of the position of the glomeruli and tubules. The tubular epithelium in the invaded areas had a granular appearance, although the nuclei were still present; many of the lumens of the tubules contained masses of a homogeneous basophilic material.

Prostate: The structure was normal except for moderate glandular hyperplasia.

Thyroid: The tissue was normal.

Esophagus: No tumor cells were seen.

Stomach: The tunica propria was diffusely infiltrated with the previously described small, dark lymphocytes. The mucosa was highly autolyzed, so that few glandular structures could be seen.

Small intestine: This tissue was highly disorganized; the mucosal structures could not be recognized. The tunica propria was packed with lymphoid tissue, but the predominant cell type was larger and lighter staining than that in the heart and kidneys and more closely resembled the tumor cell in the biopsy specimen from the face. Peyer's patches were larger than normal, and they were packed with the small, dark, lymphocytoid cells.

Large intestine: The tissue contained circumscribed lymphatic nodules, which were large and densely packed with the small, dark tumor cells.

Lymph nodes: Sections from the lymph nodes of the neck and mediastinum showed the presence of small numbers of both types of tumor cells: the small, basophilic lymphocytes, and the large, pale reticulum cell. The sections of the nodes appeared rather inactive, as compared with the lymphoid tissue of the viscera. In none of these sections was cell division encountered that in any way resembled the mitosis in the original biopsy specimen. Figure 5 is a photomicrograph of a section from a mediastinal node.

**Skeletal muscle:** A section of the right sternocleidomastoid muscle showed diffuse invasion by tumor cells.

**Bone marrow:** The specimen from a vertebra exhibited marrow spaces filled with erythrocytes, normoblasts, myelocytes and neutrophils. The cellular composition appeared normal qualitatively, but there was some increase in the percentage of lymphoid elements. The specimen of marrow from a rib was similar to that from the vertebra.

*Anatomic Diagnosis* (Dr. Bruce L. Brown).—The diagnosis was lymphosarcoma, reticulum cell type, of the periorbital tissues of the right eye, with secondary

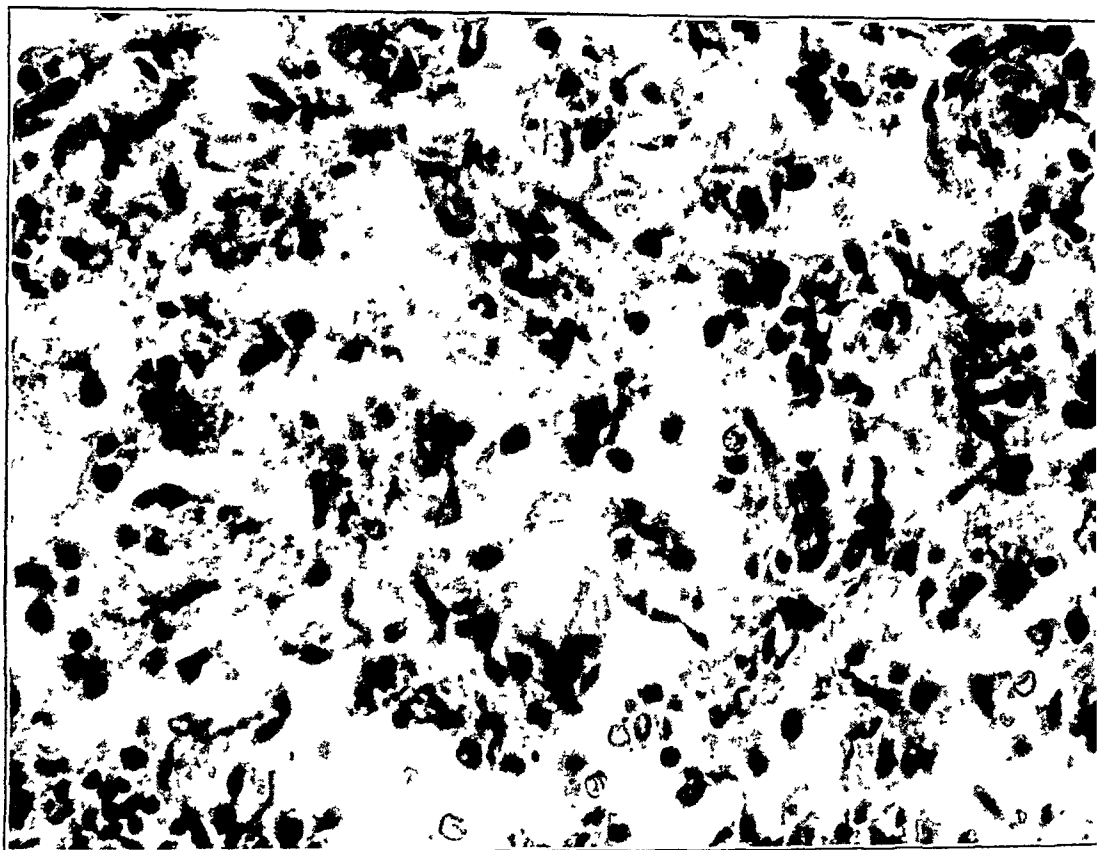


Fig. 5.—Photomicrograph of a section from a mediastinal lymph node, showing the meager involvement of the nodes.

lymphosarcomatous invasion of the lymph nodes, face, neck, heart, lungs, kidneys, liver, spleen, pancreas, stomach and large and small intestine.

*Summary.*—This case differed from 'the usual case of lymphosarcoma about the eye in a number of ways; in fact, it was characteristic in only two respects: the patient's age and sex. This neoplasm commonly occurs in the fifth decade of life and is twice as common in men as in women. The outstanding feature in this case was the time element: Only forty days elapsed from the appearance of the swelling of the lids until the patient's death; this exceedingly rapid spread from the eyelid to involve all the viscera is unusual. The early clinical

picture was confused by the presence of a foreign body and conjunctivitis in the eye, which preceded the swelling of the lid by twenty days; after hospitalization, the swelling was thought to be inflammatory until the time of the biopsy. The blood picture was not typical. Lymphocytosis is seen in a majority of cases of lymphosarcoma, but in the present case the white cell count was increased, with a normal differential count. Leukocytopenia was found on the last day of life, but this was attributed to the course of nitrogen mustard therapy. Anemia is another expected finding, especially late in the disease; in this case, however, the red cell count and the hemoglobin level continued to be fairly good to the end. A peculiarity in the behavior of this tumor was the meager involvement of the lymph nodes; lymphosarcoma, whether of nodal or extranodal origin, almost always invades the main lymph node chains secondarily; in this case the pathologic involvement of the nodes was minimal. The presence of both lymphocytes and reticulum cells in the various lesions appears contradictory, but this was seen in 25 per cent of the series of Gall and Mallory<sup>13</sup>; the occasional transition from one form to another emphasizes the close relation of the lymphocytic and reticulum cell type.

#### COMMENT

*Incidence.*—Lymphosarcoma arising in the eyelid is an uncommon tumor of the eye. Sugarbaker and Craver<sup>14</sup> analyzed 196 cases of lymphosarcoma in 1940, a twenty year collection from the tumor clinic of the Memorial Hospital for the Treatment of Cancer and Allied Diseases (all diagnoses were confirmed by biopsy); they found 1 case of primary lesion in the eyelid (0.5 per cent). Gall and Mallory<sup>13</sup> studied 618 cases of lymphoid tumors, a twenty year collection in the pathologic laboratory at the Massachusetts General Hospital; they also described 1 case of lymphosarcoma in the eyelid. McGavic,<sup>15</sup> in 1943, reported 21 cases of lymphomatoid disease involving the eye and its adnexa from the collection in the pathologic laboratory of the Institute of Ophthalmology. In this series, 17 tumors were lymphosarcomas with primary foci in the region of the eye; 3 of these tumors arose from the eyelids, and another involved the lid and orbit.

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13. Gall, E. A., and Mallory, T. B.: Malignant Lymphoma: A Clinico-Pathologic Survey of Six Hundred and Eighteen Cases, *Am. J. Path.* **18**:381-430, 1942.

14. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of One Hundred and Ninety-Six Cases with Biopsy, *J. A. M. A.* **115**:17-22 (July 6); 112-117 (July 13) 1940.

15. McGavic, J. S.: Lymphomatoid Diseases Involving the Eye and Its Adnexa, *Arch. Ophth.* **30**:179-189 (Aug.) 1943.

*Classification.*—Proof that the term “reticulum cell lymphosarcoma” does not mean the same thing to every one is seen in the reports of the incidence of this type, for whereas Warren and Picena<sup>16</sup> found reticulum cell tumor in only 3.6 per cent of 308 cases, Sugarbaker and Craver<sup>14</sup> reported the reticulum cell type in 94 per cent of 196 cases. The terminology is so varied that any author, to be understood, must first carefully define his own terms. The terms most commonly employed today are (1) lymphocytic cell type, (2) reticulum cell type, (3) giant follicle type and (4) an undifferentiated type, to designate those tumors too poorly differentiated for classification. However, Gall and Mallory<sup>13</sup> subdivided their reticulum cell tumors into “stem cell lymphomas” and “clasmocytic lymphomas” and also differentiated “lymphoblastic lymphomas” from “lymphocytic lymphomas.” This would appear to be an overclassification of such closely related neoplasms. One of the obstacles to uniformity in classification is the belief that argentaffin reticulum fibrils, so often seen in tumors of lymphoid tissue, are necessary to the diagnosis of the reticulum cell type; Rados<sup>11</sup> stated that the reticulum network is a pathognomonic feature of this type of tumor. In the Presbyterian Hospital, lymphosarcomas are designated as lymphocytic cell type when the predominant cell is small, being slightly larger than a small lymphocyte, and as reticulum cell type when the predominant cell is larger than this, usually twice as large as a lymphocyte, or even larger. The giant follicle tumors are characterized by the formation of follicles larger than is ever seen in any benign lymphomatous process. Little or no attention is paid to the presence or absence of reticulum fibers.

*Prognosis.*—Most authorities agree that the prognosis is poor for the patient with a lymphosarcoma. Sugarbaker and Craver<sup>14</sup> reported a five year survival rate of 15.9 per cent, with 10.6 per cent of the survivors free from symptoms after the five years. Stout<sup>17</sup> studied 218 cases of lymphosarcoma and reported a five year survival rate of 16.5 per cent, with 10.5 per cent of all patients apparently cured after five years. Of the treated patients, he found 21.8 per cent alive after five years, and 14.8 per cent were free from symptoms at the end of the five year period; when the follow-up period was extended to ten years, Stout found 14.6 per cent of the treated patients alive and 12.5 per cent free from symptoms. Of the untreated patients, 1, or 2.4 per cent, survived for the ten years, but at that time he possessed an obvious tumor. In their large series, Gall and Mallory<sup>13</sup> found that

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16. Warren, S., and Picena, J. P.: Reticulum Cell Sarcoma of Lymph Nodes, *Am. J. Path.* **17**:385-394, 1941.

17. Stout, A. P.: Is Lymphosarcoma Curable? *J. A. M. A.* **118**:968-970 (March 21) 1942.

their mean figure for survival was 2.0 years for the entire series; the only type of lymphosarcoma for which the mean survival rate differed significantly from this figure was the giant follicle type, for which they established the mean rate of 5.0 years. In McGavic's<sup>15</sup> series of 17 patients with lymphosarcoma primary about the eye, 11 patients were alive and symptom free at the end of four years; 4 were alive with tumor, and 2 had died. Approximate though any comparison must be, from McGavic's cases and those of Sugarbaker and Craver; Stout, and Gall and Mallory, it would appear that lymphosarcomas of the orbital region are considerably less malignant than those found elsewhere.

*Treatment.*—That there is no highly successful form of curative therapy is obvious from the survival figures just cited. It is generally agreed that untreated patients with lymphosarcoma seldom live longer than two years. Lymphosarcoma is very radiosensitive, however, and it is not at all unusual to see a bulky tumor disappear after a few days of irradiation. The results have generally been so dramatic and so superior to surgical measures that it has become almost automatic to prescribe roentgen radiation as soon as the diagnosis is made. Irradiation has even been used as a therapeutic test in establishing the diagnosis. However, evidence has been accumulated indicating that the beneficial effects of radiation are temporary. Unquestionably, there have been amelioration of symptoms and disappearance of superficial tumors, but acceptable statistical evidence that the average duration of life has been prolonged cannot be found. A new, and as yet unproved, measure in the treatment of lymphosarcoma is intravenous chemotherapy with the 2-chloroethyl amines, or nitrogen mustards.<sup>18</sup> Dramatic results against lymphosarcoma in the terminal stage have been reported by Goodman and associates<sup>19</sup> in several cases: Not only the reduction or disappearance of the lymphosarcomatous masses but also improvement in appetite, strength and weight; reduction of fever, and a new sense of well-being were observed. In general, these chemicals appear to have the same effect on lymphoid tissues as does radiation; whether they have any advantage over the use of radiation is not known at present, although they have been found effective in patients who have become resistant to roentgen radiation. The response of the tumor in the subject of this report was certainly dramatic, but the clinical response was unfortunate. Surgery, as a therapeutic measure, has nearly been abandoned, probably because most patients have spread-

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18. Gilman, A., and Philips, F. S.: The Biological Actions and Therapeutic Applications of the  $\beta$ -Chloroethyl Amines and Sulfides, *Science* **103**:409-415, 1946.

19. Goodman, L. S.; Wintrobe, M. M.; Dameshek, W.; Goodman, M. J.; Gilman, A., and McLennan, M. T.: Nitrogen Mustard Therapy, *J. A. M. A.* **132**:126-132 (Sept. 26) 1946.



ing lesions when first seen. Gall and Mallory,<sup>13</sup> however, reported an average survival of 7.0 years for a group of 23 patients who had radical operation; 10 of these patients survived an average of 6.6 years after operation without evidence of recurrence, and 13 patients survived an average of 5.7 years before evidence of recurrence appeared. Although this series is too small to offer conclusive evidence, the results appear to compare favorably with those obtained with irradiation. When one considers that lymphosarcoma about the eye tends to remain localized for some time, and weighs the danger of radiation to the eye, local excision of circumscribed tumors appears to be the procedure of choice for the ophthalmologist. If one finds evidence of further infiltration at the time of operation, the excision can be followed by irradiation of that area.

Dr. Algernon B. Reese and Dr. A. P. Stout made the diagrams of the type of tumor in this case, and Dr. Reese gave me permission to report the case.

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# INFECTION OF THE CORNEA DUE TO HERPES SIMPLEX

## An Experimental Study

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ALL HERPETIC eruptions, with the exception of those of the virus of herpes zoster, are believed to be due to the same virus. The terms herpes simplex virus, herpes febrilis virus and herpes virus refer to the same agent.<sup>1</sup> The commonest site of the herpetic lesion is on the lips, and the condition is therefore commonly referred to as herpes labialis. The genitals are not uncommonly involved in this type of lesion, and the eruption is then known as herpes genitalis. Aphthous stomatitis is frequently due to the herpes virus. Herpes cornealis is encountered frequently by the ophthalmologist in the form of herpetic or dendritic ulcer. The lesions of herpes tend to be recurrent, and some persons seem particularly predisposed to recurrent attacks. Frequently the lesions recur at the site of the primary lesion.

## GENERAL CONSIDERATIONS

### PROPERTIES OF THE VIRUS

Inoculation of human skin with vesicle fluid from any of the herpetic vesicles except those of herpes zoster results in a crop of typical vesicles of herpes simplex.<sup>2</sup> Similar inoculation of the scarified rabbit cornea produces keratitis of the herpetic type.<sup>3</sup> Herpes cornealis yields a characteristic lesion on animal inoculation. Labial herpes will produce a typical herpetic lesion on the human cornea.<sup>4</sup> Blanc and Caminopetros<sup>5</sup> passed typical lesions from herpes genitalis to the rabbit cornea and then to man. Von Sallmann<sup>6</sup> produced typical corneal lesions in rabbits from herpes-infected brain. He also passed the infection from the rabbit to the human cornea. The herpetic lesions occurring with the various febrile diseases yield a virus with the same characteristics as that

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Submitted in partial fulfilment of the requirements for the degree of Doctor of Medical Science, Columbia University.

1. Van Rooyen, C. E., and Rhodes, A. J.: *Virus Diseases of Man*, London, Oxford University Press, 1940, p. 148.

2. Teissier, P., and others: *Compt. rend. Soc. de biol.* **87**:648, 1922.

3. Grüter, W.: *Klin. Monatsbl. f. Augenh.* **65**:398, 1920.

4. Fuchs, A.: *Brit. J. Ophth.* **17**:193, 1933. Löwenstein, A.: *Klin. Monatsbl. f. Augenh.* **64**:15, 1920.

5. Blanc, G., and Caminopetros, J.: *Compt. rend. Soc. de biol.* **84**:859, 1921.

6. von Sallmann, L.: *Ztschr. f. Augenh.* **46**:217, 1921.

obtained from primary herpes.<sup>7</sup> Lipschütz<sup>8</sup> reported that the intranuclear inclusion bodies of human herpes febrilis, herpes cornealis and herpes genitalis were indistinguishable.

#### THE CORNEAL LESION

The corneal lesion is characterized by the formation of minute opacities of the epithelium, which may lead to vesiculation and necrosis and the ultimate typical picture of the dendritic ulcer. The infection may accompany herpetic lesions in other parts of the body, i. e., the lips, genitalia or skin, or may occur locally in the eye. The disease appears at all ages but is very common in childhood, before the age of 10, and is more prevalent in males.<sup>9</sup> It is usually unilateral but may involve both eyes. There is a decided tendency to recurrence.

#### CLINICAL PICTURE

The clinical picture is variable. The usual onset is acute, with pain in the eye, associated with the appearance of a haze of fine granular spots in the epithelium. This is associated with a fine bedewing of the epithelium and the development of cracks and fissures, surrounded by closely packed punctate opacities. The lesion may assume a form similar to superficial punctate keratitis or dendritic keratitis. The epithelium in the region of the lesion may lie loosely on Bowman's membrane and may be brushed away. This process is known as epitheliolysis. The appearance, therefore, is one of fine epithelial opacities, which may be followed by vesicles, under which the stroma reveals a fine haze. Vesicles are rarely seen, for soon after formation they desquamate and leave faintly clouded pits, which cause pain because the interepithelial nerve fibrillae are exposed. The vesicles are usually intraepithelial. The process may persist as such for several days or weeks and finally clear up, leaving no trace. The lesions, however, may spread and coalesce to form an irregular ulcer, the dendritic ulcer. This lesion has a characteristic appearance, as it is formed by a confluence of minute herpetic lesions in an irregular, zigzag line, with many side branchings, the ends of which have beadlike nodes. The line of ulcerations rarely exceeds 1 mm. in breadth; it shows fine furrows and is surrounded by a swollen, overhanging edge and a hazy area of infiltration. The ulcer stains readily with fluorescein, but the stain rapidly diffuses under the

7. Teissier, P., and others: *Compt. rend. Soc. de biol.* **86**:73, 1922.

8. Lipschütz, B.: *Wien. med. Wchnschr.* **71**:231, 1921; *Dermat. Wchnschr.* **73**:798, 1921; *Arch. f. Dermat. u. Syph.* **136**:428, 1921.

9. Gundersen, T.: *Herpes Corneae, with Special Reference to Its Treatment with Strong Solution of Iodine*, *Arch. Ophth.* **15**:225 (Feb.) 1936.

loose adjacent epithelium.<sup>10</sup> Reuss<sup>11</sup> beautifully demonstrated the lesion by first staining with fluorescein, allowing the green stain to diffuse, and then instilling methylene blue, which stains the actual ulcerated area deep blue.

At any time during its development the process may recede and complete healing may take place without leaving scars. Occasionally the branching processes coalesce and form lobulated, shallow ulcers. Several unconnected foci may be seen, each composed of a many branched ulcer, arranged in rosettes or in star-shaped fashion. The condition is then frequently known as stellate keratitis. Should secondary infection set in, the process may spread rapidly, with disastrous results. Rarely, even in the absence of secondary infection, there occurs a deep parenchymatous spread of the process. A circumscribed opacity develops in the stroma, and the disease is known as disciform keratitis. Grüter,<sup>12</sup> Gundersen<sup>9</sup> and others were able to isolate the herpes virus from such lesions. The process may persist for many months and ultimately clear, leaving only a faint opacification or fine, scattered facets. There may be evidence of mild iritis, with multiple recurrent extravasations.<sup>10</sup> Doerr and Vochting, cited by Lloyd,<sup>13</sup> found that the virus entered the aqueous but did not penetrate into the vitreous.

In all herpetic involvement of the cornea there is hypesthesia. In cases in which this is extreme there may develop, after the herpetic process has cleared, a condition known as keratitis metaherpetica. Here, in contradistinction to the dendritic or stellate figures, are seen small, round or oval ulcers with sinuous or scalloped borders. Gundersen<sup>9</sup> was unable to demonstrate the herpes virus in these lesions, and it is believed that they are of neuropathic origin.<sup>10</sup>

#### HISTOLOGIC FEATURES OF THE CORNEAL LESION

Histologically, the lesions show characteristic changes involving the entire thickness of the corneal epithelium.<sup>14</sup> Primarily, the nuclei become hypertrophic, and the nuclear membrane is wrinkled and thickened. The chromatin becomes agglutinated and aggregated near the membrane, and acidophilic Lipschütz corpuscles enlarge, assume a polymorphic character and appear in the nucleus. The nucleus undergoes degeneration, and diffuse necrosis develops, with swelling and vacuolation of the cells. Finally, the cornea may become completely denuded

10. Duke-Elder, W. S.: *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, vol. 2.

11. Reuss, V.: *Am. J. Ophth.* **78**:297, 1911.

12. Grüter, W.: *Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch.* **48**:319, 1930.

13. Lloyd, R. J.: *Am. J. Ophth.* **14**:601, 1931.

14. Lloyd,<sup>13</sup> Fuchs.<sup>4</sup>

of epithelium in areas, or there may remain a thin layer of flat cells surrounded by thickened, proliferated epithelium, which shows nuclear degeneration. The necrosis may involve Bowman's membrane and spread to the superficial layers of the stroma, which may show leukocytic infiltration.

The relation of the herpetic infection to the corneal nerves is not fully understood. Grüter<sup>15</sup> observed early in experimental herpetic keratitis that there were swelling and proliferation of both fine and large varicose nerve nodes. He described the appearance as similar to the main body of a branching coral.

Other investigators did not substantiate these observations. Löwenstein<sup>16</sup> could not demonstrate an affinity of the virus for fine nerve branches in the cat or rabbit. Nakajima<sup>17</sup> thought he demonstrated with the slit lamp and with vital staining irregular thickening of the nerves. This was not verified by other observers. Reiser<sup>18</sup> could find no uniform pathologic process in the nerve parenchyma. He observed that only in later stages of the keratitis were there pathologic lesions of the larger nerve fibers. He noted only an occasional single nerve trunk involved. He expressed the belief that the loss of sensitivity could not be attributed to these lesions but that the infiltration of cells around the fibers of the finer nerves caused damage to them and thereby produced hypesthesia. Reiser<sup>18</sup> observed dense accumulation of leukocytes at the limbus and marked dilatation of the lymph vessels. These congested lymph vessels were seen only in close approximation to the nerve trunks. He also noted leukocytes in perineural loose connective tissue at the limbus. He contended that the loss of corneal sensitivity was mechanical, rather than due to direct involvement of the nerves themselves.

#### SYMPTOMS

The symptoms are variable. Usually the onset is acute, with mild pain, lacrimation, photophobia and supraorbital neuralgia. The corneal sensitivity is reduced, and this is especially pronounced in the involved areas. A quiescent stage, with intermittent irritation and photophobia, follows the acute onset.

#### THE IMMUNE REACTION TO HERPES

The prevalence of recurrent attacks of herpetic lesions in man suggests that the infection did not result in significant immunity. Numerous workers have found appreciably high titers of specific antibody in

15. Grüter, W.: *Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch.* **50**:223, 1934.

16. Löwenstein, A.: *München. med. Wchnschr.* **50**:769, 1919.

17. Nakajima, M.: *Zentralbl. f. Ophth.* **24**:483, 1931.

18. Reiser, K. A.: *Arch. f. Ophth.* **139**:118, 1938; **141**:339, 1939.

the blood stream. Brain<sup>19</sup> postulated that the herpes virus stimulates an antibody response in the body and that when the antibody content falls below a certain level active herpetic lesions occur. With the titrated egg membrane technic, Burnet and Lush<sup>20</sup> found that if antibody was present at all it occurred in high titer.

Gallardo<sup>21</sup> observed that herpes-neutralizing antibodies were not found early in cases of the primary attack of dendritic keratitis. Sixteen to eighteen days after onset of the disease the blood showed definite neutralizing power against the herpes virus. In recurrent dendritic lesions the antibodies were present from the onset.

Active hyperimmunity results from repeated intradermal injections of herpes virus.<sup>22</sup> Such serum has a favorable effect in preventing herpetic infection if given prophylactically.<sup>23</sup> Passive immunity has been conferred on mice, guinea pigs and rabbits.

Gildemeister and Herzberg<sup>24</sup> found a relation between herpes and vaccinia on the basis of cross immunity tests carried out in vivo and in vitro. They demonstrated that smallpox-immune rabbits exhibited only mild reactions on injection of herpes virus. Perdrau,<sup>25</sup> Bedson and Bland<sup>26</sup> and several others were unable to corroborate these observations. They could not demonstrate any relation between the two viruses, and immunity to either infection conferred no protection against the other.

There is little evidence to support any relation between the virus of herpes simplex and that of herpes zoster. Clinically, the course of herpes zoster is more prolonged, and the bullae are considerably larger than the small vesicles of herpes simplex. Herpes zoster occurs frequently on the trunk along the distribution of a nerve, whereas herpes simplex is usually seen at a mucocutaneous junction. The vesicles of herpes zoster are subepithelial, while those of herpes simplex are intraepithelial. Pain is a predominant feature of herpes zoster, and herpes simplex is relatively painless. There is rarely a recurrence of herpes zoster, but herpes febrilis is notorious for its recurrences. The characteristic lesions of herpes simplex cannot be produced with the

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19. Brain, R. T.: *Brit. M. J.* **2**:1064, 1937.

20. Burnet, F. M., and Lush, D.: *Lancet* **1**:629, 1939.

21. Gallardo, E.: Primary Herpes Simplex Keratitis: Clinical and Experimental Study, *Arch. Ophth.* **30**:217 (Aug.) 1943.

22. Zinsser, H., and Tang, F. F.: *J. Exper. Med.* **44**:21, 1926.

23. (a) Burnet, F. M., and Lush, D.: *J. Path. & Bact.* **49**:241, 1939. (b) Bedson, S. P., and Crawford, G. J.: *Brit. J. Exper. Path.* **8**:138, 1927. (c) Zinsser and Tang.<sup>22</sup>

24. Gildemeister, E., and Herzberg, K.: *Deutsche. med. Wchnschr.* **51**:1647, 1925.

25. Perdrau, J. R.: *J. Path. & Bact.* **31**:17, 1928.

26. Bedson, S. P., and Bland, J. O. W.: *Brit. J. Exper. Path.* **9**:174, 1928.

virus of herpes zoster. However, both viruses are thought to spread by way of the nerves, and changes have been recorded in the gasserian ganglion in cases of herpes simplex and herpes zoster.<sup>27</sup> Teague and Goodpasture<sup>28</sup> produced an eruption with herpes simplex with a zoster-like distribution. Immunologic reactions lend little support to any relationship between the two viruses. Luger and Lauda<sup>29</sup> found that corneal inoculation with the fluid of zoster vesicles induced no immunity to subsequent inoculation with the fluid of herpes simplex vesicles. Netter and Urbain<sup>30</sup> found that complement fixation does not occur between zoster antigen and anti-herpes-simplex serum.

#### TREATMENT OF CORNEAL LESIONS

The treatment *par excellence* of herpes cornealis has yet to be found. The predisposition to recurrence and the possibility of development of disciform keratitis make this disease a major problem in ophthalmology. The problem has been attacked from many angles, and many workers have been encouraged by their results, but few therapeutic procedures have proved their value.

The frequent occurrence of herpetic lesions in association with malaria led some early investigators to believe that the lesion was due to toxins generated by the malarial infection. They therefore advocated the use of quinine. This form of therapy remained popular for many years, especially in countries where malaria is endemic. As recently as 1936, Selinger<sup>31</sup> advocated its use for this and other lesions of the cornea, chiefly because of the bactericidal and astringent action of quinine.

Lloyd<sup>32</sup> advocated constant patching of the herpes-infected eye and the use of radiant heat to the open eye. He recommends the "thermo-lite" or infra-red lamp held at a distance of 20 inches (50 cm.) from the eye, the skin of the lids and face being protected with towels, for periods of fifteen minutes three times a day. Hamilton<sup>32</sup> asserted that heat is directly contraindicated in any form in treatment of herpes of the cornea. It is his contention that the lesion follows pyrexia and therefore heat is to be avoided but that ice compresses are to be substituted. Fever therapy is strongly contraindicated, as it is not uncommon to see labial herpes, and occasionally corneal infection, associated with this form of therapy.

27. Howard, W. T.: Am. J. M. Sc. **130**:1012, 1905.

28. Teague, O., and Goodpasture, E. W.: J. M. Research **44**:185, 1932.

29. Luger, A., and Lauda, E.: Ztschr. f. Hyg. u. Infektionskr. **94**:206, 1921.

30. Netter, A., and Urbain, A.: Compt. rend. Soc. de biol. **90**:461, 1924.

31. Selinger, E.: Treatment of Dendritic Keratitis with Quinine Bisulfate, Arch. Ophth. **17**:1085 (June) 1937.

32. Hamilton, J. B.: Brit. J. Ophth. **27**:80, 1943.

Ultraviolet radiation has been used by some workers, with variable results. Duke-Elder<sup>10</sup> at one time thought this treatment of value but later decided that it was ineffective. Gundersen reported in 1936 that the virus of herpes cornealis could not be destroyed by any exposure to ultraviolet light that would be practical to use on the human eye.<sup>9</sup>

Darier recommended roentgen irradiation of the cornea for herpetic infection. Kumer and von Sallmann<sup>33</sup> found that even doses three times as strong as those usually recommended for the cornea had no beneficial effect in this condition.

Di Marzio<sup>34</sup> and Berud<sup>35</sup> both advocated the use of roentgen radiation. Di Marzio used 20 to 30 per cent of an erythema dose, and Berud repeated 8 per cent of an erythema dose four times directly to the cornea.

The postulation that the ever popular focus of infection plays an important role in corneal herpes has not withstood the test of time. Post<sup>36</sup> stated that all foci must be eradicated in treatment of herpes cornealis. Shapiro and Coles<sup>37</sup> reported a case of protracted dendritic keratitis that failed to respond until infected teeth were removed. Schwartz<sup>38</sup> in a series of 11 cases, reported the presence of definite foci of infection and marked improvement with their removal. Other workers have not substantiated this belief in infection as a causal agent.

Vitamin therapy has been recommended for corneal herpes. Nitzulescu and Triandaf<sup>39</sup> reported favorable responses of herpetic keratitis to use of vitamin B complex in large doses. Baird and Clay<sup>40</sup> emphasized the importance of vitamin A in the healing of all corneal ulcers, including herpes. Holden and Molloy<sup>41</sup> inactivated in vitro minimal doses of the herpes virus with synthetic ascorbic acid. Large doses had no effect in vivo in rabbits.

The advent of the sulfonamide drugs offered new possibilities in the therapy of herpetic infection of the eye. Kleefeld<sup>42</sup> stated the belief that sulfanilamide was of definite value, both therapeutically and prophylactically, in preventing recurrences of herpetic lesions. Barter<sup>43</sup> found

33. Kumer, L., and von Sallmann, L.: *Die Radiumbehandlung in der Augenheilkunde*, Rome, J. Springer, 1929, p. 130.

34. di Marzio, Q., and Salvatori, G.: *Saggi di oftal.* 5:5, 1929.

35. Berud: *Klin. Monatsbl. f. Augenh.* 83:818, 1929.

36. Post, M. H.: *Am. J. Ophth.* 12:885, 1929.

37. Shapiro, E., and Coles, H. D.: *J. Am. Dent. A.* 27:205, 1940.

38. Schwartz, F. O.: *Am. J. Ophth.* 26:394, 1943.

39. Nitzulescu, J., and Triandaf, E.: *Brit. J. Ophth.* 21:654, 1937.

40. Baird, M., and Clay, G. E.: *South. M. J.* 33:396, 1940.

41. Holden, M., and Molloy, E.: *J. Immunol.* 33:251, 1937.

42. Kleefeld, G.: *Bull. Soc. belge d'ophth.* 76:14, 1938.

43. Barter, G. A.: *Herpetic Keratitis*, *Tr. Ophth. Soc. U. Kingdom* 61:274, 1941.



no beneficial effects from the sulfonamide drugs in treatment of herpes. Improvement in 2 cases with sulfanilamide was reported by Thygeson and Stone,<sup>44</sup> but they postulated that the sulfonamide compounds are probably of no real value in herpetic infections. This belief is based on the knowledge that the sulfonamide drugs are known to be ineffective against all typical viruses. Chamberlain and Bronson<sup>45</sup> treated a number of patients with herpetic keratitis occurring as a complication of malaria. They reported significant responses to treatment with the use of sulfadiazine powder twice daily in the affected eyes.

The somewhat radical, but as yet most promising, treatment of herpetic infection of the cornea is the application of drugs directly to the cornea which destroy the infected epithelium. The postulated intranuclear location of the virus may account for the failure of most drugs. The only way that the majority of drugs could possibly act in such an infection would, therefore, be the destruction of the cell itself. Roggenkämper<sup>46</sup> and Kronenberg<sup>47</sup> advocated cauterization of the corneal epithelium with ether. The entire corneal epithelium must be briskly rubbed with a cotton applicator well soaked with ether. Other workers have not proved these results.

Hamilton<sup>32</sup> reported good results in the treatment of herpetic keratitis with the use of 2 per cent silver nitrate applied to the lids and conjunctival sac and directly to the corneal lesion with a cotton applicator. He also used pure phenol directly on the cornea, with satisfactory results, but stated that this radical form of treatment is unwarranted when adequate, and less dangerous, silver nitrate therapy is available.

Trichloroacetic acid, 50 per cent, and merbromin paste were recommended by Gifford<sup>48</sup> as cauterizing agents to be used directly on the cornea.

Probably the most satisfactory and most widely used cauterizing agent for corneal herpes is the strong solution of iodine. Gundersen<sup>9</sup> made an extensive clinical and experimental study of this condition. The author employed such therapeutic agents as alcohol, potassium iodide, hydrogen peroxide, epinephrine hydrochloride, curettage, alkalis, vaccination, paracentesis of the anterior chamber and ultraviolet radiation. The conclusions of Gundersen were that 7 per cent iodine and 5 per cent potassium iodide in alcoholic solution applied directly to the

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44. Thygeson, P., and Stone, W.: *New York State J. Med.* **43**:15, 1943.

45. Chamberlain, W. P., Jr., and Bronson, L. H., Jr.: *Herpes Simplex Keratitis in Malaria*, *Arch. Ophth.* **33**:177 (March) 1945.

46. Roggenkämper: *Klin. Monatsbl. f. Augenh.* **101**:285, 1938.

47. Kronenberg, B.: *Treatment of Herpetic Keratitis with Ether*, *Arch. Ophth.* **26**:247 (Aug.) 1941.

48. Gifford, S., in Brumer, V.: *Ocular Therapeutics*, Lancashire, England, Victor Optical Company, 1929, p. 258.

whole cornea, with resultant denuding of the entire surface, offered by far the most satisfactory results.

Eperon<sup>49</sup> advocated the use of 20 per cent zinc sulfate to cauterize serpiginous ulcers. This prompted von Sallmann and Lindner<sup>50</sup> to use a similar solution as a cauterizing agent in the Second University Eye Department in Vienna. The results were encouraging.

Iontophoresis of iodides was recommended by Verrey<sup>51</sup> for disciform keratitis, to clear the cornea and relieve pain. This effect has not been substantiated by other workers. Schnyder<sup>49</sup> used a weak solution of zinc sulfate by iontophoresis, 1 milliampere for thirty seconds, in cases of herpes of the cornea. For disciform keratitis he used a solution of iodine chloride. He claimed good results in both conditions.

Zinc sulfate, 0.25 to 0.33 + per cent, was given by Karbowsky<sup>52</sup> by iontophoresis for dendritic keratitis, with good results. Itoh-Yaeji<sup>53</sup> and Klaczko<sup>54</sup> also recommended this form of therapy.

Fisher<sup>55</sup> reported marked improvement in recurrent cutaneous herpes with weekly injections of 1:3,000 dilution of moccasin snake venom. Kelly<sup>56</sup> found moccasin snake venom of no value therapeutically in experimental herpes in rabbits. Its value in treatment of herpes cornealis is undetermined.

Methenamine<sup>57</sup> has been found to give a specific response in cases of herpes simplex on oral and parenteral administration. Buscacca<sup>58</sup> used this drug in treatment of herpetic lesions of the cornea but was unable to prove that this was the specific therapy for the condition.

The possibility of immunization against herpes simplex has been approached from different angles. Gundersen<sup>9</sup> vaccinated 8 patients with dendritic keratitis with cowpox vaccine in the usual manner, on the arm or leg, without appreciable effect on the keratitis. Four of the patients vaccinated had recurrences of the ocular lesions within two years. However, Davis<sup>59</sup> reported good results in recurrent herpes with repeated vaccination every ten to fourteen days with the vaccinia virus.

49. Schnyder, W. F.: *Klin. Monatsbl. f. Augenh.* **63**:433, 1919.

50. von Sallmann, L., and Lindner, C.: Personal communication to the author.

51. Verrey: *Bull. et mém. Soc. franç. d. opht.* **48**:99, 1935.

52. Karbowsky, M.: *Ophthalmologica* **97**:166, 1939.

53. Itoh-Yaeji: *Acta soc. opht., Japan*, no. 37, 1933.

54. Klaczko, M.: *Soviet. wiest. oftal.*, 1932, no. 1.

55. Fisher, A. A.: Treatment of Herpes Simplex with Moccasin Snake, *Arch. Dermat. & Syph.* **43**:444 (March) 1941.

56. Kelly, R. J.: Treatment of Herpes Simplex with Moccasin Venom, *Arch. Dermat. & Syph.* **38**:599 (Oct.) 1938.

57. Jaeger, K. H.: Methenamine in Virus Diseases, abstracted, *J. A. M. A.* **116**:260 (Jan. 18) 1941.

58. Buscacca, A.: *An. argent. de oftal.* **3**:3, 1942.

59. Davis, P. L.: Recurrent Herpes of the Cornea and Recurrent Herpetic Fever, *J. A. M. A.* **114**:2098 (May 25) 1940.

Gundersen<sup>9</sup> also attempted to produce higher immunity to herpes by vaccination of the lips with the virus from the patient's own dendritic lesions. He was unable to produce labial lesions, and the corneal lesions were unaffected. Other observers have reported encouraging results in recurrent herpes with repeated vaccination of skin with herpes virus<sup>60</sup> treated with dilute solution of formaldehyde U. S. P.

#### THE ANTIBIOTICS AND VIRUS DISEASES

It has been generally accepted that as a whole the antibiotics have so far proved unsuccessful in combating virus diseases. However, there have appeared in the literature a few reports of beneficial effects, some startling, on some virus diseases. Analysis of these reports for the most part reveals that only the atypical viruses have responded.

Ornithosis has been found clinically and experimentally to be susceptible to penicillin. Turgasen<sup>61</sup> and Ford and Kisport<sup>62</sup> reported excellent results in the therapy of human ornithosis with penicillin. Heilman and Herrell<sup>63</sup> found that the disease was 88 per cent fatal in untreated mice but in mice receiving 1,000 units of penicillin daily only 5 per cent died.

Psittacosis of pigeon origin was also found by Heilman and Herrell<sup>64</sup> to be 100 per cent fatal in untreated rats, but in animals treated with penicillin a mortality of only 8 per cent was observed. The virus was not eradicated by the drug, but the animals were so protected that the majority withstood the infection.

Trachoma has been reported by Sorsby,<sup>65</sup> Gilford<sup>66</sup> and others to be highly susceptible to penicillin by local and systemic application. Keyes<sup>67</sup> had negative results in 1 case. The preliminary report of Darius<sup>68</sup> on 12 cases of trachoma treated with penicillin was inconclusive. While his results were encouraging, he did not find penicillin superior to the already established sulfanilamide therapy.

Sorsby<sup>65</sup> also obtained encouraging results in inclusion blennorrhea with penicillin.

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60. Robinson, H. J., and Molitor, H.: *J. Pharmacol. & Exper. Therap.* **74**:75, 1942.

61. Turgasen, F. E.: *Human Ornithosis Treated with Penicillin*, *J. A. M. A.* **126**:1150 (Dec. 30) 1944.

62. Ford, J. L., and Kisport, R. W.: *Wisconsin M. J.* **44**:491, 1945.

63. Heilman, F. R., and Herrell, W. E.: *Proc. Staff Meet., Mayo Clin.* **19**:57, 1944.

64. Heilman, F. R., and Herrell, W. E.: *Proc. Staff Meet., Mayo Clin.* **19**:204, 1944.

65. Sorsby, A.: *Brit. J. Ophth.* **29**:511, 1945.

66. Gilford, G. H.: *Brit. M. J.* **6**:232, 1945.

67. Keyes, J. E. L.: *Penicillin in Ophthalmology*, *J. A. M. A.* **126**:610 (Nov. 4) 1944.

68. Darius, D. A.: *Am. J. Ophth.* **28**:1007, 1945.

Tyrothricin was recommended by Parker Heath<sup>69</sup> for dendritic keratitis, to be used by local instillation in the eye of a 0.5 per cent solution. Milner<sup>70</sup> found penicillin without effect in cases of disciform keratitis.

Except for these few scattered reports of success with the antibiotics, most clinical and experimental studies have proved unsuccessful. The Naval Laboratory Research Unit No. 1<sup>71</sup> tested penicillin and tyrothricin as well as tyrocidine, gramicidin, subtilin and several sulfonamide drugs and acridines, and found that none of these substances were effective in protecting mice against the influenza virus. Robinson<sup>72</sup> also found penicillin entirely ineffective against virus PR8 of epidemic influenza. Rabies<sup>73</sup> and scrub typhus<sup>74</sup> were also unaffected by penicillin.

#### PRESENT INVESTIGATION

It was the primary purpose of these experiments to determine the effect of penicillin, streptomycin and tyrothricin on the virus of herpes simplex, with special reference to its manifestations in the eye. The study was carried further in an attempt to corroborate or disprove some of the other advocated therapeutic measures. Cauterization with iodine and zinc sulfate, iontophoresis of zinc sulfate and sodium iodide, intravenous administration of sodium iodide and experiments with hyperimmune serum were carried out.

*Technic.*—White Swiss mice, weighing 8 to 10 Gm., were used for mouse passage. An injection of 0.02 cc. of emulsified infected mouse brain was made into the right cerebral hemisphere after first preparing the skin with 7 per cent alcoholic solution of iodine. A 27 gage needle and a tuberculin syringe were used for injection. The brains of dead or acutely ill mice were removed in toto after killing the animals by breaking the neck. Before removing the brain, the skin of the entire head was thoroughly prepared with 7 per cent alcoholic solution of iodine and 70 per cent alcohol. The skin was dissected with sterile instruments from the entire upper half of the skull. The exposed skull was then sterilized with iodine and alcohol, and with sterile instruments the cranial vault was dissected away, leaving the brain exposed. The brain was severed from the spinal cord and lifted from the skull to sterile containers. Brains to be kept were placed in sterile test tubes in a solution of 50 per cent glycerin, covered with paraffin and placed in the freezing unit of the refrigerator. Brains to be used for mouse or rabbit inoculation were emulsified in 2 cc. sterile isotonic solution of sodium chloride in glass tissue grinders, and the emulsion as such was used for inoculation.

69. Heath, P.: *Chemotherapy in Ophthalmology*, J. A. M. A. **124**:152 (Jan. 15) 1944.

70. Milner, J. G.: *Brit. M. J.* **7**:175, 1944.

71. Personnel of Naval Laboratory Research Unit No. 1: *Attempts to Protect Against Influenza Virus with Various Sulfonamides, Acridines, and Antibiotics*, *Science* **98**:348, 1943.

72. Robinson, H. J.: *J. Pharmacol. & Exper. Therap.* **77**:70, 1943.

73. Martin, H. L.: *Arizona Med.* **1**:323, 1944.

74. Robbins, B. H.: *Proc. Soc. Exper. Biol. & Med.* **57**:215, 1944.

Adult chinchilla rabbits were used for corneal inoculation. The eyes to be inoculated were anesthetized by instillation of drops of 0.1 per cent dibucaine ("nupercaine") hydrochloride, repeated about four times at intervals of thirty seconds, and the injection of 0.1 cc. of dibucaine hydrochloride under the insertion of the superior rectus muscle. The superior rectus muscle was then grasped with a forceps, and with a Graefe knife three vertical incisions were made in the cornea, the blade penetrating the superficial stroma. Emulsified infected mouse brain was dropped on the cornea and into the conjunctival sac and the eye gently massaged with the lids. Both eyes were inoculated at the same time, one to be used for treatment and the other as a control. In all rabbits inoculated it was possible, at the end of twenty-four hours, to detect minimal herpetic lesions along the scarifications of the cornea by examination with the slit lamp. Within forty-eight hours typical branching dendritic lesions were manifested.

The brains were checked at periodic intervals for evidence of bacterial contamination by inoculation of blood agar plates and incubation for seventy-two hours at 37 C. At no time was evidence of bacterial contamination elicited with this technic.

The strain of virus used in these experiments was obtained from J. J., a 13 year old boy with recurrent dendritic keratitis. Material was obtained from two large herpetic vesicles, one on the lower lid and the other on the upper lip, and from the infected cornea. Serum from the vesicles was aspirated with a 27 gage needle in a tuberculin syringe, 0.02 cc. being obtained from one vesicle and 0.03 cc. from the other. The vesicle fluid was diluted with 0.1 cc. of isotonic sodium chloride solution U. S. P. and inoculated (0.02 cc.) into the right cerebral hemispheres of two groups of 3 mice each. At the end of forty-eight hours all the mice evidenced signs of encephalitis. This was manifested by humped backs, ruffled fur, irritability and occasional convulsions. Within seventy-two hours all but 1 of the mice in each group were dead, and the living mouse was moribund. The living mouse was killed, and the brains of all mice were removed for storage or further passage.

With the patient under general anesthesia, the entire epithelium of the infected eye of J. J. was curetted and the material obtained from the curettage diluted with 0.1 cc. of isotonic sodium chloride solution U. S. P. This material was inoculated into the scarified right eye of a rabbit. Twenty-four hours later there was faint punctate staining along the edges of the scarifications of the rabbit cornea. At the end of a second twenty-four hour period the picture was one of typical dendritic ulcer. The ulcer healed spontaneously in a period of thirteen days.

To determine the virulence of the strain of virus being tested, four groups of 6 mice each were inoculated by successive passage. In three of the four groups there developed fatal encephalitis within three to five days. One mouse in the third group remained well and at no time demonstrated evidence of encephalitis. It can, therefore, be presumed that this strain was fatal to at least three fourths of the type mice being tested.<sup>75</sup>

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75. Andervont <sup>79b</sup> tested two strains of herpes virus in mice to determine their pathogenicity. In his series, 50 per cent of the mice tested had fatal encephalitis, and 80 per cent showed evidence of the disease. He was unable to demonstrate any change in the characteristics or nature of the virus after thirty passages of one strain and seventy-five passages of the other. The virus maintained its corneal affinity after this number of passages through mice.

Corneal inoculation of this strain of virus resulted in dendritic lesions, which were usually manifested within twenty-four hours. Occasionally at the end of this period no corneal lesions other than those produced by the scarification were seen. However, within forty-eight hours all the 30 rabbits inoculated revealed evidence of infection. The dendritic processes started in the region of the scarifications and spread in zigzag manner. As the infection progressed, isolated ulcers appeared at the periphery and in clear cornea away from the scarifications. In untreated eyes the lesions progressed for seven to nine days and then gradually subsided, and in most cases there was no further staining of the cornea after fourteen to twenty days. In some cases a superficial infiltration of the cornea persisted for several weeks, but this usually cleared, leaving only evidence of faint scarring.

The progress of the dendritic lesions was followed by staining the ulcers with 2 per cent fluorescein sodium.

*Results.*—The experimental observations are presented under the individual headings of the therapeutic agent used.

#### PENICILLIN

One cubic centimeter of emulsion of herpes-infected mouse brain was thoroughly mixed with 1 cc. of isotonic sodium chloride solution U. S. P. containing 20,000 units of penicillin per cubic centimeter. This solution was refrigerated for eight hours and the mixture shaken at frequent intervals to prevent precipitation of the brain tissue. At the end of eight hours the solution was taken from the refrigerator and allowed to warm to room temperature. Nine mice received intracerebral injections into the right cerebral hemisphere of 0.02 cc. of the solution, each mouse thereby receiving 200 units of penicillin with the injection. Immediately after the inoculation the mice became excited, and some exhibited convulsions and 3 died. Six mice withstood the primary reaction and after several hours appeared to have fully recovered.<sup>76</sup> Six control mice were given 0.02 cc. of emulsified infected mouse brain by injection. Four other controls were given intracerebral injections by the same technic of 100, 200, 300 and 400 units, respectively, of penicillin in isotonic solution of sodium chloride. All mice receiving intracerebral injections of penicillin exhibited the same type of reaction, i. e., intense excitement, irritability and convulsions. The mouse receiving 100 units of penicillin withstood the injection poorly and died within twelve hours. The others receiving penicillin alone survived and exhibited no other untoward effects after the primary reaction, which lasted only a few hours. All controls receiving emulsified infected brain

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76. Russell and Beck (Lancet 1:497, 1945) demonstrated that concentrated solution of penicillin applied directly to rabbit brain produces localized necrosis in the area so treated. Walker and Johnson (Convulsive Factor in Commercial Penicillin, Arch. Surg. 50:69 [Feb.] 1945) found that intracortical injection of penicillin in man and animals resulted in convulsions.

tissue died within three to five days, of encephalitis. The 6 mice receiving the mixture of penicillin and infected brain emulsion had encephalitis and died within four days. The brains of several mice receiving herpes virus and penicillin were removed and emulsified and reinoculated in 6 mice. Typical herpes encephalitis developed in these mice, and they died within three to five days. A group of 6 mice were inoculated by the usual technic and at the time of inoculation were given 500 units of penicillin intraperitoneally. The intraperitoneal injections of the same dose were repeated at twelve hour intervals. The course of the infection was in no way altered.

#### STREPTOMYCIN

Streptomycin was tested *in vivo* and *in vitro* in mice. One cubic centimeter of emulsion of herpes-infected mouse brain was thoroughly mixed with 1 cc. of solution of streptomycin containing 20,000 units per cubic centimeter. The solution was refrigerated for eight hours and shaken at frequent intervals to assure proper mixing. At the end of the eight hour period the solution was removed from the refrigerator and allowed to warm to room temperature. Six mice were inoculated intracerebrally with 0.02 cc. of this emulsion by the usual technic. Each mouse thereby received 200 units of streptomycin intracerebrally. All mice so treated became excited and hyperirritable and had convulsions, and 1 mouse died. Six control mice were given injections of the same herpes-infected emulsion as that used with the experimental mice, without the streptomycin. Three mice were given intracerebral injections of 200, 400 and 600 units of streptomycin, respectively. These mice immediately after injection became hyperexcitable and had convulsions, but shortly after the immediate reaction revealed no other untoward effects. All mice receiving the emulsion of infected brain plus streptomycin had encephalitis and died. However, these mice did not manifest signs of encephalitis before the third day, and 1 mouse survived for seven days and another for seven and a half days. Most of the controls manifested the disease before the third day, and all were dead in five days. Mice inoculated with the brains of those mice receiving herpes and streptomycin had herpes encephalitis and died within five days.

Fifteen mice were inoculated with herpes-infected emulsion. At the time of inoculation 6 mice were given 1,000 units of streptomycin intraperitoneally. This was followed by daily intraperitoneal injections of 1,000 units of streptomycin in two divided doses. Six mice of this group also received 1,000 units of streptomycin intraperitoneally in two divided doses, but treatment was not started until eighteen hours after inoculation. The remaining 3 mice were kept as controls. Three healthy mice were given daily intraperitoneal injections of 1,000 units of strepto-

mycin in two divided doses. All infected mice receiving streptomycin died within four days. One control survived until the fifth day, the others having succumbed within four days. The 3 healthy mice receiving streptomycin survived and exhibited no untoward effects after receiving 1,000 units of the drug for five days.

#### TYROTHRICIN

Tyrothricin, because of its known toxicity by parenteral administration,<sup>77</sup> was used only locally in the infected rabbit eye.

Both eyes of a rabbit were inoculated in the usual manner, with resultant infection manifested twenty-four hours later. A solution of tyrothricin, 33 mg. per hundred cubic centimeters, as recommended for ophthalmic therapy, was used, the treatment being started twenty-four hours after inoculation. The left eye was treated, and the right eye was left untreated as a control. Drops were instilled hourly for three doses, then every two hours for three doses and then four times a day. The dendritic ulcer spread much more rapidly in the treated eye. At the end of four days the treated eye was intensely injected, with intense swelling of the lids and conjunctiva. The cornea was deeply infiltrated, and almost the entire surface stained with fluorescein. The untreated eye was moderately injected, and the cornea revealed a rather extensive dendritic ulcer. The rabbit showed evidence of encephalitis at the end of five days and was therefore killed. A second rabbit was inoculated in similar manner. Six hours after inoculation, treatment of the right eye was started with tyrothricin, 33 mg. per hundred cubic centimeters. Drops were given hourly for three doses, then every three hours for three doses and then twice daily. Here, again, the treated eye reacted unfavorably. At the end of twenty-four hours both eyes showed evidence of early dendritic ulcers, but the treated eye was more inflamed, the conjunctiva chemotic and the cornea cloudy. Treatment was continued, and at the end of fourteen days the untreated eye had healed completely, whereas the treated eye still had a large ulcer and deep infiltration of the cornea.

To determine the effect of tyrothricin in a dilution of 33 mg. per hundred cubic centimeters on the normal rabbit eye, treatment was given to a healthy rabbit eye every hour for three doses, then every three hours for three doses and then twice a day. The healthy eye thus treated showed only slight hyperemia of the conjunctiva after six days of this treatment.<sup>78</sup>

77. Rammelkamp, C. H., and Weinstein, L.: *Proc. Soc. Exper. Biol. & Med.* 48:211, 1941. Robinson and Molitor.<sup>60</sup>

78. In view of the seemingly unfavorable results and the shortage of animal material, further experiments with tyrothricin were not carried out.



## IMMUNE SERUM

It has been shown that active immunity is readily established in animals infected with herpes virus and that animals can be protected passively with prophylactic injections of immune serum.<sup>79</sup> In the present study an attempt was made to treat established herpetic corneal infection in rabbit eyes with herpetic immune serum. According to the technic of Bedson and Crawford,<sup>23b</sup> 5 rabbits recovered from corneal lesions were inoculated intradermally every five days for four inoculations to stimulate a hyperimmune response. At the end of twenty-five days these rabbits were bled by withdrawing blood from the heart, and the serum was extracted by allowing the blood to clot and drawing off the serum. The serum was pooled and refrigerated.

Two rabbits were inoculated intracorneally by the usual technic. Twenty-four hours later beginning dendritic lesions were observed. At this time, and daily thereafter, both rabbits were given intravenous injections of 5 cc. of the pooled serum. In 1 rabbit there appeared to be a favorable response, for at the end of five days the dendritic lesions appeared to be subsiding. However, despite continued treatment, after two days the lesions again started to spread and eventually involved almost the entire cornea. The lesions were still manifest at the end of fifteen days. The second rabbit ran the usual progressive course of the dendritic ulcer, which at the end of seven days began to subside. The ulcers had healed completely at the end of twelve days.<sup>80</sup>

## SODIUM IODIDE

The reports of Thygeson<sup>81</sup> on intravenous injection of sodium iodide in treatment of human dendritic keratitis prompted an experimental study of this drug in an attempt to prove or to disprove its value.

The first experiment was to determine the effect of intravenous administration of sodium iodide on herpes encephalitis in mice. The dose of the drug to be used was arbitrary. According to the "Handbook of Experimental Pharmacology,"<sup>82</sup> 0.8 Gm. of sodium iodide per kilogram of body weight proved toxic to rabbits. Dogs tolerate 0.02 to 0.03 Gm. per kilogram of body weight. It was decided to administer one tenth of the toxic rabbit dose in proportionate amounts to mice. As the drug was to be administered intravenously, it was necessary to use larger mice, so that the injection could be made into the tail vein.

79. (a) Perdrau, J. R.: *Brit. J. Exper. Path.* 6:41, 1925. (b) Andervont, H. B.: *J. Infect. Dis.* 45:366, 1929. (c) Flexner, S., and Amoss, H. L.: *J. Exper. Med.* 41:357, 1925.

80. Because of shortage of animal material, attempt was not made to ascertain immune antigen titers.

81. Thygeson, P.: Personal communication to the author.

82. Bürg-Bern, E.: *Handbuch der experimentellen Pharmakologie*, Berlin, Julius Springer, 1927, p. 276.

Mice weighing 20 Gm. were used, and the daily dose of sodium iodide was calculated to be 2 mg.

Six mice each weighing 20 Gm. were inoculated intracerebrally with 0.02 cc. of infected brain emulsion in the usual way. At the time of inoculation and daily thereafter the mice were given intravenously 2 mg. of sodium iodide. By the end of three days all but 1 of the mice had evidence of encephalitis and were dead in five days. The living mouse at no time showed evidence of infection, and reinoculation resulted in encephalitis and death, indicating no immunity and, undoubtedly, no infection after the first inoculation. Three normal mice daily receiving 2 mg. of sodium iodide intravenously manifested no ill effects at the end of five days.

In the usual manner, both eyes of a rabbit were inoculated with herpes virus, and in twenty-four hours dendritic lesions were manifested. Beginning twenty-four hours after inoculation, 5 cc. of 10 per cent solution of sodium iodide was given daily by way of the ear vein. The corneal lesions became progressively worse, and at the end of eight days 1 rabbit died of herpes encephalitis. The corneal lesion spread, and deep infiltration became so severe in a second rabbit that the animal was killed on the ninth day. The lesions showed no tendency to heal in the third rabbit, and the animal died of herpes encephalitis at the end of ten days.

Iontophoresis of sodium iodide for disciform keratitis was recommended by Karbowsky.<sup>52</sup> An attempt was made to determine the effect of this treatment on dendritic keratitis in rabbits. The technic of iontophoresis as recommended by von Sallmann<sup>83</sup> was employed. The modified van Heuven tube as cathode was placed on the cornea, the rim fitting the limbus and being filled with a 1 per cent solution of sodium iodide. The anode was held on the back of the rabbit's head, which had been shaved. The application was employed for five minutes at 2 milliamperes of galvanic current with local anesthesia induced with 0.1 per cent dibucaine hydrochloride. Eighteen hours after treatment the eye showed considerably greater inflammatory reaction and more extensive corneal involvement than the untreated eye. The treatment was repeated after eighteen hours at 2 milliamperes for three minutes, and again in six hours. The treated eye reacted badly. There was profuse discharge, the lids were swollen and the conjunctiva was chemotic; and there was a large, deep-staining ulcer of the cornea. The untreated eye showed a typical dendritic ulcer of moderate severity. Treatment was discontinued in this eye, and two cathode iontophoretic treatments at twenty-four hour intervals with 1 per cent sodium iodide for three minutes at 2 milliamperes were given to the previously untreated eye.

83. von Sallmann, L.: *Am. J. Ophth.* **25**:1292, 1942.

Here, again, the reaction was unfavorable, as the eye became intensely inflamed, the dendritic ulcer spread rapidly and the cornea became deeply infiltrated. All treatment of both eyes was discontinued and the ulcers healed within three weeks, leaving dense central leukomas. The experiment was repeated on 2 more rabbits, but the iontophoresis was continued for only two minutes at 2 milliamperes of current. In 1 rabbit the treated eye reacted unfavorably and the lesions spread more rapidly and the infiltration was deeper and more extensive than in the untreated eye. The third rabbit tolerated the treatment considerably better. There was slightly greater spread of the lesions and slightly more infiltration of the stroma. The untreated eye was completely healed in twelve days and the treated eye in thirteen days.

#### IODINE

Gundersen<sup>o</sup> found that cauterization of the entire corneal epithelium with 7 per cent iodine and 3 per cent potassium iodide the most satisfactory method of treatment for human dendritic ulcer. Experimentally he found that the treatment was poorly tolerated by the rabbit cornea. An attempt in this study was made to determine the effect of a weaker solution of iodine on the herpetic lesion of the rabbit cornea. Five rabbits were tested in this series. Forty-eight hours was allowed to elapse between the time of inoculation and the institution of treatment. In each rabbit only one eye was treated, the other being kept as a control. All treatment was done with the animal under dibucaine anesthesia, and an alcoholic solution of 3.5 per cent iodine was used as a cauterizing agent. Immediately after the administration of iodine to the eye 70 per cent alcohol was applied to neutralize the action of the iodine. The eyes were then copiously irrigated with isotonic sodium chloride solution U. S. P. In 2 rabbits only the existing dendritic lesions on the cornea were treated. The lesion was briskly rubbed with 3.5 per cent iodine on a cotton applicator and then the region touched with alcohol and the eye irrigated with saline solution. Twenty-four hours later the areas treated were found to be completely denuded of epithelium and the underlying stroma densely infiltrated. Fresh dendritic lesions appeared in previously clear cornea, and as they were noted they were touched with iodine. The lesions continued to spread, and the denuded areas were deeply infiltrated and very slow in epithelizing. Healing was definitely retarded in the treated eyes, and the scarring was much more extensive than in the untreated eye.

In the other 3 rabbits of this series forty-eight hours after inoculation the entire cornea was briskly rubbed with 3.5 per cent iodine and alcohol and then irrigated, with the result that the entire cornea was denuded of epithelium. The treated eyes showed much more inflammatory reaction, and the cornea became densely infiltrated. The

untreated eyes healed within fourteen to fifteen days, while healing was delayed until twenty-eight to thirty-five days in the treated eyes and these eyes were left with dense central leukomas.

#### ZINC SULFATE

Zinc has had widespread use in ophthalmology. It has been used in concentrated solution as a cauterizing agent<sup>50</sup> and in weak solution by iontophoresis.<sup>84</sup> The latter method was used clinically by von Sallmann, with unsatisfactory results.<sup>72</sup> Schnyder and Karbowski recommended the use of 0.25 to 0.33 + per cent solution by anode iontophoresis. Both the methods were tested experimentally.

A rabbit was inoculated in the usual manner in both eyes. Twenty-four hours later typical dendritic lesions were observed. With dibucaine anesthesia, zinc sulfate, 0.25 per cent, was given by iontophoresis for two minutes at 2 milliamperes. As it was desired to drive the zinc ions into the cornea, the anode was employed on the eye and the cathode on the shaved head of the rabbit. Twenty-four hours later the entire cornea was denuded of epithelium and the stroma deeply infiltrated. Healing was greatly retarded, for the untreated eye healed within fourteen days, whereas the treated eye did not heal for twenty-one days and the eye was left with a dense corneal scar. Because of the unfavorable clinical reports of von Sallmann and the poor experimental result in 1 rabbit, to save animal material the experiment was not repeated.

A series of experiments were carried out with the use of 20 per cent zinc sulfate as a cauterizing agent on the infected rabbit cornea. Seven rabbits were tested in this series. Both eyes were inoculated, one to be treated, the other to be kept as a control. The eyes were treated in twenty-four hours in 3 rabbits, but not for forty-eight hours in the remaining 4 animals, as their lesions were minimal.

Three rabbits received extensive treatment to one eye. The eyes were anesthetized with dibucaine and the dendritic lesions stained with fluorescein. Zinc sulfate, 20 per cent, was applied liberally to the lesions and to the surrounding corneal epithelium. The zinc sulfate was well rubbed into the epithelium, and the eyes were then irrigated with isotonic sodium chloride solution. The following day the eyes were again stained with fluorescein, and the cornea was found to be denuded in the treated areas. One eye revealed a few fresh dendritic lesions, and these were again treated with 20 per cent zinc sulfate immediately. A second rabbit revealed fresh lesions in the treated eye four days after the original treatment, and these areas were again treated. The results of these treatments were as follows: The rabbit receiving the second treatment

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84. Karbowsky.<sup>52</sup> Schnyder.<sup>49</sup>

after four days revealed no evidence of staining lesions in the treated eye nine days after the original inoculation. The untreated eye did not heal until the thirteenth day. In the rabbit receiving the second treatment on the following day the treated eye did not heal until after twenty-five days, whereas the untreated eye healed within fifteen days. The rabbit receiving only the original treatment had healing of both eyes on the fifteenth day.

The other 4 rabbits received treatment with 20 per cent zinc sulfate only to the localized dendritic lesions. The eyes were anesthetized with dibucaine and then stained with fluorescein to demonstrate the lesion on the cornea. A pointed applicator tightly wound with cotton was dipped in 20 per cent zinc sulfate and squeezed almost dry, so that only the localized lesions themselves were cauterized with the solution. The applicator was rubbed firmly into the epithelium. The following day the eyes were again stained with fluorescein and examined. The area immediately surrounding the treated area was denuded of epithelium and stained deeply. It was necessary to treat 2 eyes again because of fresh lesions which occurred three days after the original treatment in 1 eye and on the first and second day in the other eye. The other 2 rabbits showed no evidence of recurrence after the original treatment. In all 4 of these rabbits the treated eyes healed appreciably sooner than the untreated controls. The eye requiring the treatment to be repeated twice was healed in ten days and the control eye in fourteen days. The other eye requiring repetition of treatment was healed in ten days and the control eye in eighteen days. In the other 2 rabbits the treated eyes healed in fourteen and fifteen days, whereas the untreated controls did not heal until the nineteenth and twenty-first days, respectively. The treatment with 20 per cent zinc sulfate was fairly well tolerated by the rabbit eyes. After treatment there were denuding of the epithelium in the treated area and slight infiltration of the stroma, which cleared with the healing of the eye.

Of the 7 rabbits treated with 20 per cent zinc sulfate, 5 showed definite improvement after the treatment. In 1 rabbit the treatment seemed to make no difference in the time required to heal the dendritic lesions. The treatment appeared to be definitely detrimental to the healing of dendritic ulcer in 1 rabbit.

#### COMMENT

Review of the vast literature on herpes simplex, with special reference to its manifestations in the eye, revealed that extensive studies have been made concerning the virus. While many properties are well understood, others remain obscure. The infection is prevalent and widespread and definitely recurrent. Recurrences are precipitated by a wide variety of unassociated conditions. Infection results in immunity, which is

transient or insufficient to prevent recurrences. In the human subject there apparently is no local tissue immunity.

The ocular infection of herpes simplex is sufficiently prevalent and destructive to make this a therapeutic challenge to the ophthalmologist. The problem has been attacked by many earnest workers, from a wide variety of approaches. There is no known specific therapy for the herpes virus.

The antibiotic drugs penicillin, streptomycin and tyrothricin were used experimentally in this study on animals and were found to be relatively ineffective against the herpes virus. Their powers in combating certain secondary infections cannot be denied. They cannot, however, be considered the treatment of herpetic infection of the cornea.

It has been proved that active and passive immunity can easily be established in experimental animals. However, from these tentative experiments it appears that hyperimmune serum has little therapeutic effect against the established corneal infection in rabbits.

Experiments in animals with sodium iodide given systematically and introduced into the eye by iontophoresis did not bear out the claims of its advocates.

Until a therapeutic agent that is specific for the virus of herpes simplex and is nontoxic to human tissue can be found, one must depend on measures that will destroy the organism and produce only minimal tissue damage. Probably the most widely used agent is the strong solution of iodine, which destroys the virus but in so doing cauterizes and destroys the corneal epithelium. This treatment is usually well tolerated in the human eye but is definitely contraindicated in the rabbit eye. Use of 20 per cent zinc sulfate as a cauterizing agent on the infected cornea was found to be beneficial in treatment of the experimental infection in the rabbit and to be well tolerated by the eye.

### CONCLUSIONS

1. (a) Penicillin is ineffective in combating the virus of herpes simplex *in vivo* and *in vitro* in mice.

(b) Penicillin in concentrated solution is an irritant when applied locally to the brain.

2. (a) Streptomycin in high concentrations seems to have a slight inhibitory effect on the virus of herpes simplex *in vivo*. It fails, however, to destroy the virus completely.

(b) Systemic administration of streptomycin has practically no effect on herpes encephalitis in mice.

(c) Streptomycin is an irritant when applied locally in high concentration to the brain of mice.

3. Tyrothricin in dilution of 33 mg. per hundred cubic centimeters is not a beneficial therapeutic agent, but has an unfavorable effect on herpetic infection of the eye of the rabbit.

4. Hyperimmune serum is relatively ineffective in the treatment of dendritic keratitis in rabbits.

5. Intravenous use of sodium iodide is ineffective in combating herpes encephalitis in mice and has no beneficial effect in dendritic keratitis in rabbits.

6. Cathode iontophoresis of 1 per cent solution of sodium iodide has a definitely detrimental effect on herpetic infection of the rabbit cornea.

7. Local application of 3.5 per cent iodine and 70 per cent alcohol to herpes-infected eyes of rabbits delays healing and results in greater scarring.

8. Anode iontophoresis of 0.25 per cent zinc sulfate is contraindicated in dendritic keratitis in the rabbit.

9. Cauterization of dendritic ulcers with 20 per cent zinc sulfate is of definite value in the healing of these lesions in rabbit.

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# INVASION OF THE OPTIC NERVE BY RETINOBLASTOMA

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IN 1931<sup>1</sup> I published the results of a microscopic study of the incidence of invasion of the optic nerve by retinoblastoma. The report was based on a series of 119 enucleated eyes containing retinoblastoma. In 53 per cent of the eyes the tumor had extended into the optic nerve beyond the lamina cribrosa. In 43 per cent of the eyes the optic nerve was not severed at operation beyond the tumor extension, and, therefore, residual tumor had been left in that portion of the nerve remaining in the orbit. Thus, in 43 per cent of the cases a recurrence in the orbit and fatal termination were to be expected unless measures were directed against the residual tumor left in the nerve at the time of operation. The globes from which these statistics were gleaned were enucleated between the years 1878 and 1929, a period of fifty-one years.

For some time I have felt that these figures are not consistent with current cases. Therefore, a similar study was made of 116 eyes enucleated between the years 1934 and 1947, covering a period of thirteen years. In this series, the tumor had extended into the optic nerve beyond the lamina cribrosa in 27 per cent, and beyond the site where the nerve was severed at operation in 8.5 per cent. Therefore, in the older series the tumor extended beyond the lamina cribrosa in 1 out of 2 eyes, and in the more recent series, in 1 out of 4 eyes (table). Earlier recognition of the lesion, more accurate differential diagnosis and prompt enucleation must account for the lower incidence of nerve invasion in the more recent series.

In the older series, of the eyes showing extension of the tumor beyond the lamina cribrosa, the nerve was severed at operation beyond the extension in only 1 out of 5, while in the more recent series this was accomplished in 2 out of 3 eyes (table). This difference must be due to the surgeon's fuller consciousness of the importance of obtaining a long nerve at operation and his closer attention to execution. In the older series the short nerves were conspicuous, averaging usually only 1 mm. or so in length, while in the more recent series the nerves were much longer.

The lower mortality figures now, as compared with those of many years ago, also reflect the earlier diagnosis and the longer optic nerve

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From the Institute of Ophthalmology of the Presbyterian Hospital.

1. Reese, A. B.: Extension of Glioma (Retinoblastoma) into the Optic Nerve, *Arch. Ophth.* 5:269-271 (Feb.) 1931.



stump obtained at the time of enucleation. Hirschberg,<sup>2</sup> in 1869, reported 5 per cent cures, and Wintersteiner,<sup>3</sup> in 1897, 13 per cent cures. The Army Institute of Pathology<sup>4</sup> showed approximately 50 per cent cures in 1939, based on 121 cases.

It is rare for the tumor to extend into the optic nerve beyond the lamina cribrosa for more than a few millimeters, and extremely rare for it to extend as far as 8 to 10 mm. If the tumor has extended into the nerve for a distance of approximately 10 mm., it will gain access to the subarachnoid space at the site where the central vessels leave the nerve. When the tumor reaches the subarachnoid space, it spreads rapidly to the chiasm and the brain. Occasionally the tumor reaches the subarachnoid space around the optic nerve without extending back as far as the exit of the central vessels. In 1 instance the tumor extended into the nerve sheath after passing the lamina cribrosa and spread in the subarachnoid space beyond the operative section. In 2 instances the tumor reached the optic nerve sheath without invading the nerve itself.

*Extension of Retinoblastoma into Optic Nerve*

	1878-1929 119 Eyes	1934 to Date 116 Eyes
Extension of tumor into optic nerve posterior to lamina cribrosa	63 eyes, or 53%	32 eyes, or 27%
Operative section of nerve beyond tumor extension.....	12 eyes, or 19% of the 63 eyes	22 eyes, or 70% of the 32 eyes

In approximately 10 per cent of the cases the tumor extended out of the globe by way of the sclera. This presupposes choroidal invasion and occurred usually by way of the emissaria in the presence of extensive growth, or in the presence of buphthalmos and its attendant distention and thinning of the scleral walls.

Tumor invasion of the nerve begins in the base of the physiologic or glaucomatous cup around the central vessels; in 3 specimens tumor cells could be seen in the lumen of one of these vessels. The tumor invaded the choroid in about 25 per cent of the cases, and the rich vascular channels here offer another entrée of cancer cells to the blood stream.

The size of the tumor in the globe does not seem to have a direct bearing on whether or not the tumor extends into the nerve. Sometimes the tumor is small and shows a nerve extension.

2. Hirschberg, J.: Anatomisch Untersuchungen über Glioma retinae, Arch. f. Ophth. **14** (pt. 2):30-102, 1868.

3. Wintersteiner, H.: Das Neuroepithelioma retinae, Vienna, Franz Deuticke, 1897.

4. Army Institute of Pathology: Personal communication to the author.

Retinoblastoma arises from the nuclear layers of the retina and is a tumor, therefore, of nerve tissue origin. It appears to have a certain affinity for invading nerve tissue, such as that of the optic nerve bundles. This happens so literally at times that the size and the shape of the bundles, surrounded by their septums, are preserved, with the tumor tissue occupying the place of the nerve fibers. The tumor has little tendency to invade fibrous tissue, as evidenced by the fact that when the optic nerve is atrophic the hypertrophied septal tissue appears to be a barrier to invasion of the nerve, and by the fact that retinoblastoma spreads through the sclera to the extraocular structures only exceptionally (10 per cent), and then late in the presence of extensive growth.

From time to time there have been advocates<sup>5</sup> of the combined intracranial and orbital operation for retinoblastoma.<sup>6</sup> It is my feeling that the rationale of this operation is based on false premises. The operation is a logical procedure, based on the available information in the literature. Unfortunately, this information is not altogether correct. Some of the advocates of this combined operation have been motivated by the figures published by me in 1931.<sup>1</sup> The main purpose of the present paper is to correct these figures with current cases, which show, as previously discussed, a much lower incidence of nerve extension.

Furthermore, the literature<sup>7</sup> states that retinoblastoma proves fatal because of intracranial extension by way of the optic nerve. On the basis of Merriam's analysis<sup>7a</sup> of the autopsies performed in 15 of our

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5. (a) Ray, B. S., and McLean, J. M.: Combined Intracranial and Orbital Operation for Retinoblastoma, *Arch. Ophth.* **30**:437-445 (Oct.) 1943. (b) Jean, G. W.: Discussion of Glioma of the Retina, *ibid.* **51**:505 (Sept.) 1922. (c) Glioma of the Optic Nerve: Correspondence, *J. A. M. A.* **100**:1793 (June 3) 1933. (d) Dott, N. M., and Meighan, S.: Intracranial Resection of the Optic Nerve in Glioma Retinae, *Am. J. Ophth.* **16**:59, 1933. (e) Rand, C. W.: Glioma of Retina: Report of a Case with Intracranial Extension, *Arch. Ophth.* **11**:982-994 (June) 1934. (f) Shannon, C. E. G.; Jaeger, R., and Forster, F. M.: The Combined Intracranial and Orbital Operation for Bilateral Retinoblastoma, *Tr. Am. Ophth. Soc.* **42**:326-333, 1944.

6. The accepted procedure in the combined intracranial and orbital operation for retinoblastoma is first to perform the cranial operation by excising the intracranial portion of the nerve between the chiasm and the optic foramen. The best worked-out technic has been published by Ray and McLean,<sup>5a</sup> and this includes coagulation of the optic nerve at the optic foramen and the insertion of a plug of muscle tissue over this site. Twelve to thirteen days later the enucleation is done, at which time the entire orbital portion of the nerve is removed, along with the globe.

7. Leber, T.: Die Geschwulstbildungen der Netzhaut, in Graefe, A., and Saemisch, T.: *Handbuch der gesamten Augenheilkunde*, Leipzig, Wilhelm Engelmann, 1916, vol. 7, pp. 1723-1943. Adam, C.: Statistisches, Klinisches und Anatomisches über das Glioma retinae, *Ztschr. f. Augenh.* **25**:330-350, 1911.

7a. Merriam, G. R.: Retinoblastoma: An Autopsy Analysis of 15 Cases, to be published.

cases of death from retinoblastoma, it appears that retinoblastoma more frequently proves fatal by distal metastases than it does by extension into the cranial cavity. In 9 of Merriam's 15 cases, or 60 per cent, there were blood-borne distal metastases—to the bones in 7 cases (46.7 per cent), to the viscera in 6 cases (40.0 per cent) and to the lymph nodes in 6 cases (40.0 per cent). In only 9 of the 15 cases had intracranial extension occurred via the optic nerve, and in 7 of these there was generalized leptomeningeal involvement. Thus it can be seen that retinoblastoma is much more than a local disease which jeopardizes life only by extension to the cranial cavity via the optic nerve.

The advocates of the combined intracranial and orbital operation must conceive of the tumor as invading the optic nerve and extending backward within the confines of the nerve to the intracranial cavity. The examination of eyes with retinoblastoma shows that the usual extension into the optic nerve proper is only for a few millimeters posterior to the lamina cribrosa, and that an extremely rare occurrence is its extension as far back as 10 mm. If the tumor extends into the nerve for approximately 10 mm., it then gains access to the subarachnoid space at the site where the central vessels make their exit from the nerve. After the tumor reaches the subarachnoid space by this route, or by direct extension from the optic nerve into the subarachnoid space, it then spreads rapidly throughout the subarachnoid space, not only of the involved optic nerve but of the chiasm and elsewhere throughout the cranium. This is the manner in which the tumor may reach the cranium, and not by extension through the substance of the optic nerve to the intracranial portion of the nerve and to the chiasm, and hence to the brain. Thus, when the tumor reaches the subarachnoid space and travels in the manner described here, an excision of the intracranial portion of the nerve will probably not be beyond the intracranial extension of the tumor.

In this recent series of 116 eyes with retinoblastoma enucleated since 1934, only 10, or 8 per cent, showed that the operative section was not beyond the tumor extension into the nerve. In all probability this figure could be lowered appreciably if the surgeon had secured an adequate portion of nerve at the time of the enucleation. It is rare indeed for the tumor to extend as far as 10 mm. into the nerve, and certainly there is no reason for an optic nerve to be shorter than 10 to 12 mm. when an eye harboring a retinoblastoma is enucleated.<sup>8</sup>

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8. Almost any length of nerve may be secured at operation if the following procedure is practiced: Pass a heavy silk traction suture through the insertion stumps of the internal and external rectus muscles, engaging some of the adjacent sclera. When the optic nerve is cut, pull the globe forcibly outward with the traction sutures, placing the optic nerve on a stretch, and at the same time press the blades of the scissors backward along the nasal wall of the orbit.

Furthermore, if the tumor has extended into the nerve as far as 10 mm., it probably already has reached the subarachnoid space, where it spreads rapidly, and would probably be beyond the site where the nerve would be excised in the case of an intracranial operation. If, by chance, the case happens to be one in which the operative section was not made beyond the tumor extension into the nerve proper, this fact should be available within forty-eight hours if the optic nerve is prepared as biopsy material and examined microscopically.<sup>9</sup>

I therefore believe that, on the basis of the arguments presented in this paper, there is no justification for the combined intracranial and orbital operation for retinoblastoma.

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9. The optic nerve should be severed from the globe flush with the sclera immediately after the enucleation. Sections for microscopic study should be cut from the proximal, distal and central portions of the nerve to determine whether there has been tumor extension and, if so, whether or not the operative section has been made beyond it.

## CLINICAL COURSE OF OCULAR COMPLICATIONS OF ARACHNODACTYLY

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IT IS the general belief that the dislocations of the lens and the rigid iris seen in arachnodactyly are nonprogressive, congenital defects. Observations on 21 patients over periods of five to fourteen years and on 25 others for shorter periods have convinced me that many are true abiotrophies. While some patients complain only of reduced visual acuity, others show progressive dislocation of the lens, with uveal degeneration ending in detachment of the retina. Knowledge is far from complete, and only a single eye of this type has been examined in the laboratory. This article is offered in the hope of attracting other case reports.

The disease is inherited as a dominant in many families and as a recessive in others. A parent with normal eyes and some of the skeletal defects may transmit the disease in complete form, and the same is true of a parent with normal skeleton and congenital bilateral dislocation of the lens. It is not unusual to find a parent with some of the features of the disease, a child with all the typical defects, another child with hands and feet only characteristic of the condition and other children who are normal or rather tall and thin. Isolated cases are occasionally seen, but it should be assumed that every case of bilateral congenital dislocation of the lens is one of arachnodactyly until the family has been studied thoroughly.

The arachnodactylic infant may be as plump as the normal child, with no other abnormality at the time but dislocation of the lens and abnormal flexibility of some joints. This child grows tall and very thin by the fifth year and in the teens may become very tall, but is never of the pituitary type. One such patient (E. C., among the individual cases reported) reached 6 feet 8½ inches (204.5 cm.) by the fourteenth year, and another grew from 5 feet 7½ inches (171 cm.) to 6 feet 1½ inches (187 cm.) in two and one-half years (M family). The feet are so long and narrow that difficulty is experienced in getting shoes to fit. Size 12½ AA was used by a 12 year old boy.

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Read at the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 6, 1947.

Occasionally a typical case is seen in a very short person. The father of a very tall boy was 5 feet 4½ inches (164 cm.) in height but presented typical features of the disease in every other detail, with the lenses well out of place, a defect which attracted attention to the family.

The normal broad pelvis may be found in affected female patients, with considerable subcutaneous fat on the lower portion of the torso,



Fig. 1.—The father is 5 feet 4 inches (162.5 cm.) in height, and the son, 5 feet 7½ inches (171 cm.). The son grew 6 inches (15 cm.) in two and one-half years.

which is out of all proportion to the thin chest, narrow shoulders, long thin fingers and abnormal height. Scoliosis is common but does not appear until the teens. A tall, thin child may fill out well at puberty, and this is especially true of girls. A deep midsternal groove is seen, which in exceptional cases is so deep that the heart is displaced to the left. A transverse depression at the lower part of the thorax is probably due to traction of the diaphragm, to which the weak bony structures yield. Horner's syndrome has been reported, with a smaller breast on the same side in females and with the hooked little finger,

defects which are also seen in syringomyelia and which lead one to think that all are due to damage to the trophic nerve cells about the central canal of the spinal cord in the embryo. The span of the out-

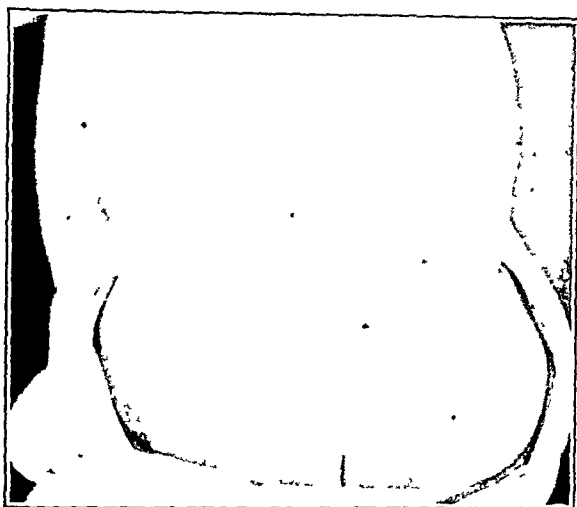


Fig. 2.—Broad, female type of pelvis and abundant subcutaneous fat on the torso of woman with arachnodactyly, bilateral dislocation of the lens and retinal detachment. The patient was referred by Dr. H. M. Gurley.



Fig. 3.—Hands and feet of patient shown\*in figure 2, with typical defects of arachnodactyly.

stretched arms, from one finger tip to the other, should not be more than the height, but in these patients it often exceeds the normal by several inches, resembling the normal stature of apes. Abnormal flex-

ibility of joints may be evident in infancy and is a source of entertainment among children. The skeletal changes do not usually appear until the third to the fifth year and, because of gradual development, often escape notice. When the child goes to school, the defect in vision is discovered, and the patient is brought to an oculist, who finds the dislocated lenses. The youngest child with this defect whom I have seen was 15 months old, but the defect is considered congenital. The effort to improve vision with lenses may be difficult because the child is often mentally slow or actually defective. It is easy to overlook displacement of the lens of lesser degrees unless the pupil is widely dilated to expose some part of the outline of the lens. Almost without exception, the dislocations are upward and outward. Somewhat later than normal, the patient begins to read and may acquire an education, even with vision of 10/50 in one eye. This defective vision may improve as he grows older. Despite the low visual acuity, the patient may read with little difficulty, doing it in his own way. When the child is 10 years of age, the observer can usually tell whether the defect belongs to the favorable group of congenital abnormalities or to the abiotrophies, with positive pathologic changes and a poor prognosis. Visual acuity gives a good idea of the future, as improved vision implies moderate dislocation of the lenses and absence of uveal degeneration. Children with poor vision usually have progressive displacement of the lens, associated with atrophy of the tapetum far forward, sclerosis of the choroidal vessels, opacities in the vitreous and pigment on strands of the vitreous and the suspensory ligament of the lens. The iris is aplastic, with good color and well developed pupillary margin; but the bold network on the surface, derived from the vascular capsule, is missing and the fibers are all radial. Occasionally poor vision is present without a satisfactory explanation. It has been assumed that poor vision was due to dislocation of the lenses, but there are usually other reasons, which require careful consideration before removal of the lens. Detachment of the retina occurs after slight injury, after operation or spontaneously. There has been much argument as to which operation was safest—needling or removal of the lens. Needling is difficult, and absorption is slow and incomplete. Detachment has followed removal of the lens and also has occurred spontaneously. Some surgeons use the loop to remove the lens; but if an iridectomy is done, the lens should float up into the wound without difficulty even if well out of place. If an iridectomy is not done, prolapse of the iris follows and recurs after replacement. The lens is rounder than normal because of relaxed lenticular fibers, and the specific gravity and weight are subnormal because of underdevelopment. One lens of this type (De V. family) snapped back into the



eye, with subsequent hemorrhage, an event suggesting a persistent hyaloid artery.

Cowan and Spaeth suggested iridectomy to expose a lens-free area. The results they have obtained compel serious consideration of this procedure.

It is my opinion that any operation is hazardous, because of the faulty construction and lowered vitality of the eyes of these patients, and that the type of operation is not significant.

The uveal changes have been seen in children of 10 years, but many escape notice until adult life. Atrophy of the tapetum appears first in the extreme periphery of the retina, with large clumps of pigment here and there and sclerosis of the choroidal vessels. Pigment granules can be seen on the strands of vitreous, the fibers of the suspensory ligament and even in the hyaloid fossa, if the lens has moved out. Floaters develop in the vitreous, and the lens is displaced into the anterior chamber or, more often, into the vitreous. The spastic iris atrophies, becomes rigid and will not respond to atropine. If the pupillary area is free, the slit lamp shows ragged strands of vitreous waving in and out of the pupil as the lids sweep across the eyeball. At this stage, slight accidents occasion retinal detachment, which may have existed unobserved if located far forward or if the pupil is small and the vitreous cloudy. The lens may be dislocated into the anterior chamber, and 3 eyes of 2 patients of this series were operated on for that reason. More often the lens falls back on the floor of the fundus and in time becomes opaque. If the displacement of the lens exposes a clear portion of the pupil, vision may be improved for a time. A person with arachnodactyly with lenses in normal position may show the uveal degeneration already described. It is impossible to predict the rate of progress, but in this group blindness has occurred as early as 14 years, and as late as 35 years, of age. The oldest patient with good vision in one eye was 54 years of age. The case histories are reported as family groups, together with a number of individual cases.

#### CASE HISTORIES <sup>1</sup>

##### DE V. FAMILY (OCTOBER 1932)

*Grandfather*: Not seen, but evidently the transmitter.

*Father*: Normal eyes; delicate bony structure with scoliosis.

*Mother*: Normal eyes; typical skeleton, hands and feet.

*Daughter*: Normal.

*Son*: Normal.

*Daughter* (aged 18): Typical complete case. Vision with correction 10/40 and 10/30. Atrophy of peripheral tapetum with clumps

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1. Affected members are designated by italics.

of pigment; pigment on fibers of suspensory ligament; beginning sclerosis of choroidal vessels.

June 4, 1945: Vision with correction; perception of moving objects and 10/40; lenses dull and cloudy; irises smooth and without character; detachment far forward in right eye.

*Daughter* (aged 13): Typical complete case. Vision with correction 10/30 and 10/70. Pigmented, atrophic areas peripherally; sclerosis of choroidal vessels; lenses cloudy; beads of pigment on fibers of suspensory ligament.

March 2, 1943: Operation (Dr. Moehle) for retinal detachment in left eye and reoperation, without success.

*Son* (aged 9): Typical complete case. Vision 10/200 and 10/70 with —8.00 D. sph. Beads on fibers of suspensory ligament and strands of vitreous waving in and out of pupil; view of fundus difficult.

May 21, 1943: Removal of lens (Dr. Moehle) from right eye to improve vision; lens snapped back into eye, with hemorrhage into vitreous and loss of vision.

July 15, 1947: Right eye blind, soft and painful; ciliary injection; pupil large and fixed, with opaque, organized mass in vitreous. Left eye: Vision 8/200, not improved; lens cloudy, with only a small bit of pupil free at extreme periphery temporally.

*Son* (aged 5): Typical complete case. Patient did not read or cooperate; irises smooth; denses dislocated up and out.

May 31, 1945: Vision 10/200 and 10/15, with correction. Both pupils lens free; pigment on strands of vitreous and posterior corneal surfaces; advanced choroidal atrophy in both eyes, with much pigment in clumps; height 6 feet 4½ inches (194 cm.); patient wears no. 12 shoe.

*Comment.*—This family has been under observation fourteen years. The mother, with normal eyes but typical skeletal defects, transmitted the disease to 4 of 6 children. The uveal changes were found in all the affected children. Operation was performed on 1 child to improve vision and on another to correct retinal detachment, without success in either case.

#### P. FAMILY (SEPTEMBER 1935)

*Mother* (aged 33): Incomplete case.

R. E.: +5.50 sph.  $\subset$  +2.50 cyl., axis 90 = 20/20

L. E.: +7.00 sph.  $\subset$  +0.50 cyl., axis 30 = 20/20

Lenses in normal position; broad, female pelvis, with typical hands and feet.

*Father*: Normal.

*Daughter* (aged 9½): Typical complete case.

R. E.: +10.00 sph.  $\subset$  +2.00 cyl., axis 105 = 20/70

L. E.: + 8.00 sph.  $\subset$  +2.00 cyl., axis 75 = 20/70

Jaeger type 5 and 7 with correction.

May 1942: Vision 10/30 and 10/100 with correction. Right eye: Jaeger type 1. Left eye: Blind; lens well back in vitreous, opaque; loose strands waving in and out of pupil.

March 1944: Both lenses on floor of fundus; atrophy of tapetum, exposing pale choroidal vessels; irises atrophic.

R. E.: +9.00 sph.  $\ominus$  +1.50 cyl., axis 90 = 20/33 (?)

L. E.: +10.00 sph.  $\ominus$  = 10/200

July 1946: R. E.: +9.00 sph.  $\ominus$  +1.50 cyl., axis 90 = 20/25 (?)

L. E.: +10.00 sph. = 10/100

(Contact lenses give 20/33? and 10/70)

*Daughter* (aged 10): July 1946: Vision normal; typical skeleton, hands and feet.

*Daughter* (aged 13): Normal.

*Child* (aged 19): Not seen.

*Comment.*—The transmitter (mother) has an atypical condition, but has 1 daughter with the typical disease and another with an atypical form. The condition would not have been discovered in either the mother or the second daughter if the examination of the oldest daughter had not been made and a search for other cases in the family begun. Two children escaped. The family has been under observation eleven years.

#### K. FAMILY (OCTOBER 1935)

*Grandfather*: Not examined, but from photograph and the son's statement, it would seem he had the typical disease.

*Father* (aged 33): Typical case.

R. E.: Vision 5/200, not improved.

L. E.: Vision 10/200; with  $-1.00$  sph.  $\ominus -6.50$  cyl., axis 120 = 20/25. Right pupil partly free of lens; little displacement of left lens. Dilation showed displacement of left lens. Pigment on strands of vitreous and suspensory ligament.

January 1943: Right lens dislocated into anterior chamber; pain severe; moderate redness; tension 25 mm. (McLean). Lens removed; vision 10/40, with correction. Wound opened from within two months later. Wound reopened; flap jumped over incision. No relief from pain; anterior chamber collapsed; posterior scleral trephination; enucleation. Epithelial invasion of anterior chamber.

*Mother*: Normal.

*Daughter*: Typical case. Killed in automobile accident. Vision with correction 20/200 in each eye (Dr. Ohly's clinic).

*Daughter* (aged 7½): Typical case.

R. E.:  $-6.00$  sph. = 10/40

L. E.:  $-5.50$  sph. = 10/70

Patient walked at age of 18 months; congenital deafness; first teeth at age of 10 months.

October 1940: With correction patient reads Jaeger type 2 and 6. No changes in fundus and no deposits of pigment.

February 1942: Dr. James Smith removed left lens to improve vision; resulting vision 10/30, with ability to read Jaeger type 5 with correction. Later, detachment of retina; poor result from diathermy.

April 1945: Right lens dropped down, leaving clear pupil and vision 20/33 with +11.00 sph.  $\subset$  +2.00 cyl., axis 105. Vision in left eye 10/100.

*Comment.*—This family has been under observation twelve years. The father had typical skeletal characteristics and displaced lenses. The better eye had little displacement and no other pathologic change, with good vision. The right eye had been lost through epithelial invasion after removal of the lens. The chief complaint was pain, with no increase of tension until collapse of the chamber. Two daughters were affected. The living child had operation for improvement of vision, with fair temporary result. Later, the retina became detached and diathermy was given, without success. The father's condition was found after the daughter came to the clinic for glasses to improve vision.

#### M. FAMILY (JANUARY 1938)

*Father* (aged 45): Typical complete case, but height only 5 feet 4 inches (163 cm.) and weight 147 pounds (66.7 Kg.); wears no. 8 shoe. Vision 10/30 and 10/20 with correction. Tension 15 and 18 mm. (McLean).

May 1942: Vision 10/100 in each eye. Lenses dropped down, covering both pupils.

May 1943: Vision 10/50? in each eye; tension 25 mm. (McLean).

June 1944: R. E.: Pupil lens free; +16.00 sph.  $\subset$  +2.00 cyl., axis 90 = 10/15 with ability to read Jaeger type 2.

L. E.: Vision not improved.

*Mother*: Normal.

*Son* (aged 13): Typical complete case. Corrected vision 10/50 and 10/40. Height 5 feet 7 inches (170 cm.); reads Jaeger type 1 and 3 with difficulty.

May 1943: Height 6 feet 1½ inches (187 cm.); patient wears no. 11 shoe.

October 1945: Vision 10/70 and 10/40 with correction; Jaeger types 1 and 8 read with difficulty. Irises smooth and without characteristic change; no sign of uveal degeneration other than pigment on strands of vitreous. Left eye has the freer pupillary area.

*Son* (aged 11): Normal.

*Son* (aged 8): Normal.

*Comment.*—This family has been under observation nine years. The father was short but otherwise had typical defects. He had fair vision until the lenses dropped down; after more complete luxation, vision improved in one eye. The growth of the affected son in two and one-

half years, from 5 feet 7 inches to 6 feet 1½ inches, is noteworthy. The father's condition would have escaped notice if the son with the typical disease picture had not applied for improvement of vision.

#### F. FAMILY (FEBRUARY 1940)

*Father* (aged 51): Hypermetropic astigmatism but lenses in normal position; definite skeletal characteristics.

*Mother* (aged 48): Normal.

*Daughter* (aged 19): Normal

*Daughter* (aged 18): Typical complete case.

R. E.: -10.00 sph. = 5/200; Jaeger type 12 with correction.

L. E.: -10.00 sph. = 10/50.

July 1945: R. E.: -9.00 sph. = 10/200.

L. E.: -9.00 sph. = 10/50.

With reading correction, vision nil (R. E.) and Jaeger type 13 (L. E.).

Pigment attached to vitreous strands; albino fundi, hair light brown; irises smooth and without features usually present.

*Son* (aged 15 months): Fine, plump infant; both lenses displaced up and out.

*Daughter* (aged 15): Normal.

*Son* (aged 14): Normal.

*Daughter* (aged 11): Normal eyes; typical hands and feet.

*Son* (aged 7): Normal.

*Comment.*—This family has been under observation seven years. The father, with hypermetropic astigmatism and skeletal defects, transmitted the defect to one daughter in complete form, and her child, at 15 months of age, has bilateral displacement of the lens. Another daughter has normal eyes but typical hands and feet.

#### REPORT OF INDIVIDUAL CASES

CASE 1.—S. S., aged 17 years; typical case. Left lens removed by Dr. E. C. Place, without complications. No improvement in vision. Family not studied.

*Comment.*—No explanation for the poor vision was found.

CASE 2.—E. C., aged 14 years; typical case (Dr. J. H. Ohly).

January 1936: Height 6 feet 8½ inches (204.5 cm.); weight, 165 pounds (74.8 Kg.); span, 6 feet 11½ inches (212 cm.); no. 11½ shoe. Correction of + 11.00 sph. gives vision of 10/70 and perception of large objects in respective eyes. Pupils rigid; opacities in vitreous; atrophy of tapetum. Right lens cannot be found; left lens opaque, on floor of fundus; vitreous strands waving in and out of pupils. Fingers "double jointed"; spinal curvature. No family history obtained or study made.

CASE 3.—A. F., aged 6 years.

January 1936: Dislocation of lenses but bony features not pronounced.

June 1936: Dr. Irving Jacobs removed both lens from anterior chamber, with excellent results.

December 1941: Vision with correction 20/20 and 20/25; Jaeger type 1.

March 1945: Patient timid and mentally retarded. Vision with correction 20/33 in each eye. Iris atrophic; thinning of tapetum peripherally, vitreous strands waving in and out of pupils.<sup>2</sup>

*Comment.*—The only successful operations were performed in this case. Pathologic signs were present nine years after the operation.

CASE 4.—Miss E., aged 38; normal lenses but typical skeletal defects.

February 1942: Vision 20/20 with corrections of  $-10.00$  and  $-9.50$  sph. for the right and left eyes, respectively. Peripheral fundus showed tapetal atrophy, with choroidal vessels losing color.

October 1946: Vision with correction 20/25 in each eye.

*Comment.*—Uveal degeneration in a patient with normal eyes, with typical skeletal defects and myopia.

CASE 5.—Mr. S., aged 20; typical skeletal changes. Right lens normal; vision 20/20 with  $+1.50$  sph.  $\subset +3.00$  cyl., axis 90. Left lens down on floor of fundus, opaque; anterior chamber deep, view of fundus impossible because of small, rigid pupil and opacities in vitreous. Height, 6 feet  $2\frac{1}{2}$  inches (189 cm.); weight, 155 pounds (70.3 Kg.);  $10\frac{1}{2}$  AA shoe. Left eye lost vision, without injury or inflammation, six years ago.

*Comment.*—The better eye was hypermetropic, with astigmatism, but was otherwise normal. The patient has been under observation four years, with no change in his condition.

CASE 6.—Paul B. July 1937: Typical case, referred by Dr. W. M. Howard. Vision with correction 10/50 in each eye; read Jaeger type 5 when held close to eyes

December 1944: Dr. Howard reported on patient at age of 13. Vision with correction 20/50 and 20/70. Lenses had not changed position. Patient was wearing low minus astigmatic lens and was doing well at school. No other case has been found in his family.

*Comment.*—This case shows how well a patient with only fair vision can do at school.

#### SUMMARY

The ocular lesions of arachnodactyly have been regarded as malformations, but many are true abiotrophies, with progressive changes in the uvea. We have attributed the poor vision to malposition of the lens, but there are other, more serious, causes. The eyes with the more serious defects do not withstand operation or injury. In the present series, 12 operations were done on 7 eyes of 6 patients. Three operations were done on 3 eyes of 3 patients to improve vision, without attaining the object; and 1 of these eyes was operated on again for subsequent retinal detachment, without success. Eight operations were performed to save 4 eyes of 4 patients from disaster. A man

2. This case has been reported elsewhere (Am. J. Ophth. 20:1042, 1937).

aged 40 (Mr. K.) underwent operation on the poorer eye for removal of the lens from the anterior chamber, with temporary success. Three operations followed, the last an enucleation, which the pathologist's report of "epithelial invasion of the anterior chamber" explains. A child of 6½ years was operated on by Dr. Irving Jacobs for bilateral dislocation into the anterior chamber, with an interval of six months between operations; and excellent vision resulted, the only successful outcome in the series. Another patient was operated on twice for detachment of the retina, without benefit.

In eyes with good vision the course is uneventful, as the displacement of the lens and the uveal changes are minimal and neither is progressive. The prognosis for eyes with poor vision is not good because of associated progressive changes in the uvea and the tendency to complete dislocation of the lens and retinal detachment.

Operation to improve vision should be done only after the most careful examination, as there are usually other reasons for the defective vision besides dislocation of the lens. The usual rule to operate on the poorer eye may not hold in such cases, for vision in one eye is usually very poor, even in the more favorable cases.

The ophthalmologist will be asked whether a patient with this defect should marry, but he often is not able to decide whether the heredity in a particular case is *dominant* or *recessive*.

A patient with some of the skeletal features may pass the blight in complete form to most of the children (De V family). An apparently normal person with dislocated lenses may do likewise.

Every case of bilateral congenital dislocation of the lens should be considered as one of arachnodactyly until it has been shown otherwise. Since finding the first case of this series, in 1932, I have seen but 1 case of dislocated lenses without clear evidence of arachnodactyly in the family.

#### DISCUSSION

DR. FRANK D. CARROLL, New York: C. C. Clarke (*Ectopia Lentis*, ARCH. OPHTH. 21:124 [Jan.] 1939) analyzed the records of 31 patients with congenital dislocation of the lens treated at the Vanderbilt Clinic. He concluded that the best procedure in cases requiring surgical intervention was preliminary iridectomy followed by a loop extraction of the lens. This was performed on 10 eyes, without operation complications interfering with sight.

I have reviewed the records of 7 patients with arachnodactyly not previously reported. One of them was an intelligent woman in her twenties, who was over 6 feet (180 cm.) tall. Her lenses were dislocated up and nasally in each eye, and she obtained 20/30 vision with her aphakic correction. Three patients were infants treated by the pediatricians and never examined by an ophthalmologist. Two of these had congenital heart disease, which is commonly associated with arachnodactyly. The third was born with contracture of the hands,

feet and knees. This condition has improved somewhat during the past ten years, but plastic surgery will probably be necessary. Two sisters, both mentally retarded, had this syndrome. One died at the age of 6 years; the other had both lenses removed by loop extraction, and cyst of the iris developed after operation in one eye and was treated by the injection of iodine. Another patient, besides arachnodactyly and ectopia lentis, had congenital cardiovascular disease with a dissecting aneurysm, a complication previously reported in the literature, and a calcified astrocytoma in the occipital lobe. After the operation on the brain, an iridectomy was performed on the right eye. This was followed by detachment of the retina. With a high myopic correction he has useful vision in the left eye. The last patient, although only 12 years of age, had the typical appearance of patients with this syndrome; with a high myopic correction vision in her eyes is 2/200 and 20/30.

DR. RALPH I. LLOYD, Brooklyn: Since 1932, when I became interested in this condition I have almost always been able to find positive evidence of arachnodactyly in other members of the family, and I know of but 1 case of congenital dislocation of the lenses in which there was any doubt of the occurrence of arachnodactyly in the family. If the patient has congenital dislocation of both lenses but a normal skeleton, that person can be the parent of a child with a completely typical syndrome; but the reverse is also true.



# LIPEMIA RETINALIS ASSOCIATED WITH ESSENTIAL HYPERLIPEMIA

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AND

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**L**IPEMIA retinalis was first described by Heyl<sup>1</sup> in 1880. The condition is known to occur in cases of hyperlipemia when the fat in the blood is sufficiently emulsified to become visible in the retinal vessels. The hyperlipemia that is associated at times with alcoholism, phosphorus poisoning, pneumonia, peritonitis and starvation has never been known to become ophthalmoscopically visible. Duke-Elder<sup>2</sup> underlined the statement that "diabetes is the only disease wherein the condition becomes sufficiently marked to be seen ophthalmoscopically in the retinal vessels." Duke-Elder also noted the one exception to this, the case reported by Wagener,<sup>3</sup> in 1922, of a 9 year old boy with leukemia who had undergone radiation treatment. Since its first description, in 1880, about 60 cases of lipemia retinalis have been reported in the literature, and it is noteworthy that all these have been of diabetic patients, usually in the younger age groups. Since in all the reported cases the patient was either approaching or in a state of coma, it has been assumed that acidosis necessarily exists. Thus, in a recent textbook, Tassman<sup>4</sup> expressed agreement that acidosis is apparently a factor and that the condition is seen in young diabetic patients when the lipid content of the blood rises above 5 per cent. However, Lepard,<sup>5</sup> reporting a case in 1936, noted that acidosis was

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1. Heyl, A. G.: *Tr. Am. Ophth. Soc.* **3**:54, 1880.

2. Duke-Elder, S. W.: *Textbook of Ophthalmology*, vol. 3, St. Louis, C. V. Mosby Company, 1941.

3. Wagener, H. P.: *Am. J. Ophth.* **5**:521, 1922.

4. Tassman, I. S.: *The Eye Manifestations of Internal Diseases*, St. Louis, C. V. Mosby Company, 1946.

5. Lepard, C. W.: *Lipemia Retinalis in the Nondiabetic Patient*, *Arch. Ophth.* **32**:37 (July) 1944.

not a factor, nor did the patient have diabetes. Holt and his co-workers<sup>6</sup> also reported the condition in a case in which the diagnosis of idiopathic lipemia had been made. The case of Lepard is also assumed to be one of idiopathic hyperlipemia, and both the patients were young children. Kauffman<sup>7</sup> in 1943 reported a case of lipemia retinalis in a man aged 25; this case he considered the fourth reported instance of the disease in a nondiabetic person, Wagener's case being the first. The diagnosis in Kauffman's case was chronic gastritis and chronic alcoholism. Although these 4 cases are the only ones reported in the ophthalmologic literature, there has been occasional reference to the retinal picture in the pediatric literature in cases of idiopathic hyperlipemia. Goodman and his co-workers,<sup>8</sup> describing the clinical picture of idiopathic hyperlipemia in a 1 year old child, commented that the eyegrounds were consistent with the picture of lipemia retinalis. It is noteworthy, therefore, that most of the instances of nondiabetic lipemia retinalis, uncommon as they are, were noted in association with the condition called idiopathic, or essential, hyperlipemia. This condition is primarily a pediatric disease and is probably due to a familial defect or an anomaly of lipid metabolism. Holt<sup>6</sup> suggested that hyperlipemia may occur in cases of hepatic disease in which conditions are such that the fat metabolism is not impaired but the internal utilization of fats is interfered with. The main change in the blood serum is the increase in the amount of the neutral fat. So far as it is known, the case to be presented represents the fifth recorded instance of lipemia retinalis seen in a nondiabetic person, and is probably the first reported case of the condition in a nondiabetic adult.

#### REPORT OF A CASE

A white man aged 55 was admitted to the Veterans Administration Facility because of recurring pains in the lower substernal region and epigastric "burning," which was not relieved with antacids. There was no complaint of visual disturbance. Routine physical examination revealed normal skin; no xanthomatosis; an enlarged liver, palpable 3 fingerbreadths below the costal margin; a normal spleen, and a blood pressure of 100 systolic and 60 diastolic.

Samples of blood had the appearance of a creamy emulsion. The Wassermann and Kahn reactions of the blood were negative. The fasting blood sugar, determined on three occasions, was 113, 85 and 116 mg. per hundred cubic centimeters. The glucose tolerance test gave normal results. The serum amylase was 104 mg. per hundred cubic centimeters; gastric analysis gave normal results, and the urine was negative for albumin and sugar. Roentgenograms of the chest, the long bones and the skull revealed nothing significant; the roentgenographic series of the gallbladder was normal. The electrocardiogram was normal. In marrow obtained by sternal

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6. Holt, L. E.; Aylward, F. X., and Timbus, H. G.: Idiopathic Lipemia, *Bull. John Hopkins Hosp.* **64**:279, 1939.

7. Kauffman, M. L.: Lipemia Retinalis, *Am. J. Ophth.* **26**:1205, 1943.

8. Goodman, M., and others: Idiopathic Lipemia, *J. Pediat.* **16**:596, 1940.

puncture, an abundance of large cells was observed, the cytoplasm appearing foamy. Biopsy of the liver revealed large amounts of fat in the cells. (A detailed clinical report by the medical department will be made elsewhere.)

Vision was 20/20 in each eye, without glasses. The anterior segment was normal. The fundus revealed the typical appearance of advanced lipemia retinalis. Its general appearance was striking. The vessels, arteries and veins were flat and ribbon like. They appeared to be filled with cream. The color of the arteries was similar to that of the veins, so that the vessels in their course from the disk could not be distinguished very far out into the periphery. The light reflex was absent from the surface of the vessels. There was no perivascular infiltration. Differentiation of veins and arteries was made possible only by noting the relative difference in caliber, the veins maintaining a ratio to the arteries of 3:2. The rest of the fundus was a homogenous, pale cream color. The color of the disk appeared to be lighter but within normal limits. At this stage, analysis of the blood serum revealed that the total lipid content was 13.13 per cent and the cholesterol 1,128 mg. per hundred cubic centimeters.

The patient was then placed on a low fat diet, and within five days the fundus was noted to change from a pale cream to a light salmon color. The color of the vessels was also seen to have undergone definite changes. Examination of the vessels for a distance of 1 disk diameter from the papilla revealed that the arteries were a bright red and the veins the usual dusky, deeper hue. The light reflexes in this portion of the retina were also considered normal. The vessels peripheral to this point also showed a return to normal color, but to a much lesser degree. Although veins and arteries could be distinguished from each other, there was a notable decrease in brightness of the light reflexes, and the color was definitely less decided than that of the vessels near the disks. A sample of blood taken at this stage revealed the total lipid content to be 4.06 per cent and the cholesterol 665 mg. per hundred cubic centimeters. A few days later the sample of blood contained 2.12 per cent total lipids and 443 mg. of cholesterol per hundred cubic centimeters. Examination of the fundi at this time revealed a generalized rosy red color of the eye-grounds. The vessels appeared to be normal in color from disk to periphery. The ratio of the caliber of the veins to that of the arteries was 3.2. The light reflexes were normal, and the previous appearance of "flatness" of the vessels was absent. The low fat diet was discontinued and within five days there occurred what was called a gastric crisis, i. e., severe gastric cramps. Examination of the fundi at this time again revealed the typical textbook picture of lipemia retinalis. The fundi were seen two days before the occurrence of the gastric crisis, and at this time the peripheral portions of the vessels were much paler than normal, although the portions within 3 disk diameters of the papilla were fairly normal. The retinal condition never returned to its original textbook picture, as the patient soon learned that he felt better when he was on a low fat diet.

A sample of blood was sent to Dr. S. J. Thannhauser, of Boston, who verified the previous findings and corroborated the clinical diagnosis of idiopathic hyperlipemia. His observations are compared with the normal values in the following tabulation.

Lipid Constituents	Amount, Mg./100 Cc.	
	Patients	Normal
Neutral fat.....	3,440	6-150
Total phospholipids.....	188	180-250
Total cholesterol.....	550	150-260
Free cholesterol.....	230	40- 70
Cholesterol esters.....	320	70- 75
(58 per cent of total)		

## SUMMARY

Severe lipemia retinalis was seen in a man aged 55 whose condition was diagnosed as idiopathic hyperlipemia. At the time of his admission the blood serum revealed a fat content of 13.13 per cent. When, with a low fat diet, the blood lipid content fell to 4.06 per cent, the hyperlipemia was seen to recede. When the fat content of the blood fell to 2.12 per cent, the condition of lipemia retinalis was observed to be absent. When the patient returned to a regular diet, the blood lipids were again elevated, to 4.7 per cent, and the condition of lipemia retinalis reappeared.

## CONCLUSIONS

Although acidosis may usually be associated with hyperlipemia, as noted in diabetic persons, it is not an important factor in the production of the lipemia retinalis which occurs in the condition known as idiopathic, or essential, hyperlipemia.

The condition of lipemia retinalis may occur with a normal carbohydrate metabolism.

It is noteworthy that the condition of essential hyperlipemia occurs in infants and young children. This may account for the paucity of reports in the literature concerning the fundi, as relatively few cases will have the benefit of an ophthalmologist's consultation.

It is felt that the condition known as idiopathic, or essential, hyperlipemia affords a field for the continued study of lipemia retinalis, and it is urged that all patients with such a condition be given a thorough ophthalmologic study. The case reported here is thought to be the first reported instance of essential hyperlipemia in an adult. The cause of the condition is still quite unknown.

The case presented was from the medical service of Dr. M. F. Koszalka and Dr. J. J. Levin. Dr. S. J. Thannhauser and Miss Grace Ballard, of the Mount Sinai Hospital, Milwaukee, gave assistance in the laboratory studies.

238 West Wisconsin Avenue.

## Notes and News

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### GENERAL NEWS

The following lectures in ophthalmology will be delivered at the Royal College of Surgeons of England, in Lincoln's Inn Fields, London, W.C. 2, England:

Tuesday, March 29, 1949: A. Franceschetti (professor of ophthalmology, University of Geneva), "Cataract Associated with Lesions of the Skin"; G. B. Bietti (professor of clinical optics, Pavia University), "Protein and Amino Acid Deficiencies in Ophthalmology."

Wednesday, March 30, 1949: Prof. E. Hartmann, "Psychosomatic Symptoms in Ophthalmology," and H. J. M. Weve (professor of ophthalmology, Rijksuniversiteit), the subject to be announced later.

### SOCIETY NEWS

**Ophthalmological Society of the United Kingdom.**—The annual congress will be held at the Royal Society of Medicine, 1 Wimpole Street, London, W. 1, on March 31 and April 1 and 2, 1949. The subject under consideration will be "Corneal Grafting"; the discussion will be opened by Dr. R. Townley Paton, New York; Prof. A. Franceschetti, Geneva, Switzerland; Prof. G. P. Sourdille, Nantes, France, and Mr. J. W. Tudor Thomas, Cardiff, Wales.

The rest of the program will appear later. The annual dinner will be held on March 31. For further information, apply to Mr. G. J. O. Bridgeman, 45 Lincoln's Inn Fields, London, W.C. 2, England.

**Central Illinois Society of Ophthalmology and Otolaryngology.**—At the meeting of the Central Illinois Society of Ophthalmology and Otolaryngology in November, the following officers were elected: president, Clifton S. Turner, M.D., Peoria, Ill.; president elect, Harold Watkins, M.D., Bloomington, Ill.; vice president, Meredith Ostrom, M.D., Rock Island, Ill., and secretary-treasurer, Philip R. McGrath, M.D., Peoria, Ill.

### PERSONAL NEWS

**Prof. Joseph Meller's Festschrift.**—To celebrate Professor Meller's seventy-fifth birthday a collection of scientific articles is planned. As at present the number of contributions to German periodicals is necessarily limited, articles will be acceptable for the *Festschrift* which have appeared in any periodical provided the article was printed with the dedication to Dr. Meller's seventy-fifth birthday. Reprints of such original articles could then be bound in one volume and could serve as a *Festschrift*. Notice of such an article should be sent to Prof. J. Böck, Augenlinik, Graz, Austria.

# Society Transactions

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SOCIÉTÉ FRANÇAISE D'OPHTALMOLOGIE

Annual Meeting, May 18-22, 1947

The French Society of Ophthalmology held a successful second postwar meeting in Paris, May 18 to 22, 1947. A number of foreign ophthalmologists attended. The western hemisphere was represented by Castroviejo, of New York, and Busacca, of São Paulo, Brazil. The Belgians and Swiss were numerous, as usual. The Italians appeared on the scene again, and two Polish colleagues, Szymanski and Kapuscinski, emerged from the other side of the iron curtain. Nordenson was there and Zeeman, and, of course, Arruga. There was an important British contingent, with Law, Doggart, King, Maccallan and Mathewson, and a single ophthalmologist from Dublin.

The meetings were held every morning; in the afternoon there were operations in the Paris hospitals and visits to the Pasteur Institute and to the National Institute for the Blind. The International Council of Ophthalmology and the International Association for the Prevention of Blindness held their meetings in Paris during the same week.

On Sunday, May 18, the papers dealt mostly with adnexa of the eyes. There were two papers, by Fritz and Bonhomme, on contact lenses, and the moot subject, at least in Europe, of relations between the physician and the manufacturer of contact glasses was discussed. Guillaumat, and others, spoke on what they call "relative hemianopsia"; in some patients in whom no defect can be detected on the tangent screen there is a difference in the visual perception of two identical objects shown simultaneously in the normal and in the abnormal half of the field. In the reviewer's opinion this is akin to the phenomenon of sensory suppression of Bender and Teuber (*Nystagmoid Movements and Normal Perception*, *Arch. Neurol. & Psychiat.* 55: 511-529 [May] 1946).

On Monday, May 19, papers dealt mostly with diseases of the cornea, conjunctiva and lens. Busacca gave an account of his investigations on the conjunctival lymphatics with vital injections of trypan blue. There was a long discussion on the etiology of trachoma, started by Nataf, who is one of the early champions of the role of the rickettsias; Busacca, of course, had something to say about this, but no undisputable conclusion was reached. Bietti showed some interesting photographs, taken in Rome during the war, with a German electronic microscope. One could distinctly see a number of very small round bodies; there is a possibility that these may be the agents of trachoma. Castroviejo presented two excellent colored films, one on cataract extraction and the other on corneal transplantation. There was a general and interesting discussion on the latter subject. Paufigue and Sourdille are to prepare the 1948 symposium of the society on this subject. Paufigue had been able to remove the eye of a patient who died of pneumonia a few months after receiving a partial, nonpenetrating transplant, and his photographs showed how the grafted tissue is accepted by the host. In cases of intracapsular cataract extraction in which the lens capsule is taut and

the forceps is unable to get a hold, Sédan makes a minute puncture in the capsule and a small amount of liquid is allowed to escape; after this the capsule forceps can get a purchase.

On Tuesday, Professor Bonnet, of Lyon, presented the annual symposium for 1947, which was devoted to ophthalmoscopic study of the fundus in diseases of the blood, such as leukemia. This study had been published in book form a few weeks earlier, as is the custom with the French Society of Ophthalmology. It is a magnificent contribution to our specialty; there are 75 illustrations in color, 47 in black, and 263 pages of text. It is not possible to present an abstract of this symposium, but a study of Bonnet's book will be found worth while.

On Tuesday evening there was the traditional dinner, with toasting and speech making. Marigot de Treigny, the secretary of the French Society of Ophthalmology, welcomed the numerous foreign members present that night, and a considerable number of the latter answered.

The papers presented on Wednesday, May 21, dealt mostly with diseases of the fundus. Franceschetti stressed the value of chorioretinitis in the diagnosis of toxoplasmosis. Fritz showed that not only the retinal arteries but also the veins are important in the diagnosis and prognosis of general diseases. Amsler, in photographs taken at different times in the same patients, was able to demonstrate that retinal hemorrhages will travel more than one suspects and that in their shift downward they will by-pass the macula. Sourdille read an excellent paper on the various types of operation for glaucoma; Weekers told of his satisfactory results with nonpenetrating cyclodiathermy in uveitis with secondary hypertension. Rouher had something to say about the treatment of retinal edema by intravenous injections of procaine. This treatment has been widely used in France in the last few years, and often successfully, particularly in cases of arterial spasm.

On the last day, Thursday, Weekers read an interesting paper on his studies of critical fusion frequency. There is a frequency threshold for the perception of a steady light, but this threshold varies with the state of the retina and of the optic nerve fibers; when they are not normal, the perception of a steady light will be possible, even with slower flashing. Weekers was able to study this on the whole surface of the field; not only is the diagram thus traced similar to that of the field mapped in the usual way, but anomalies, in early glaucoma for instance, can be detected in this way earlier than in any other. Verrey spoke of his work on the cytology of the aqueous in several diseases of the eye, and the meeting came to an end with an excellent paper by Guillaumat and Gilles on roentgenography for detection of foreign bodies in the eye, with a new and accurate method devised by Porcher.

I regret that this report of the meeting, with its fifty-seven papers and lengthy discussions, is necessarily sketchy and incomplete.

May I suggest to our American confrères that attending the meeting of the French Society of Ophthalmology in Paris in May can be both interesting and pleasant? The society has a considerable number of non-French members; there are at present 18 Americans, and many more would be welcome; finally, Paris in May is usually at its best.

E. HARTMAN.

## Book Reviews

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**Neurosurgical Pathology.** By I. Mark Scheinker, M.D. Price, \$8.75. Pp. 355, with 238 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1948.

This book is a concise, interesting and easily read presentation of the pathology of cerebral disease as it confronts the neurosurgeon. In essence, the volume consists of (1) a discussion of changes produced by trauma to the head and spinal cord, and (2) a description of the various cerebral neoplasms and their prominent clinical manifestations.

The opening chapter is devoted to the author's concept of cerebral edema and its role in producing intracranial pressure. This chapter offers the neuro-ophthalmologist much thought-provoking material and opens avenues for explanation of a number of anomalous circumstances associated with choked disk (low pressure at lumbar puncture; small tumor causing high intracranial pressure). Even those who do not subscribe entirely to the author's physiologic concepts must accept the reasonableness of the argument on the basis of present knowledge.

Pathologic changes which occur after nonpenetrating injury to the central nervous system are interpreted in terms of the concepts outlined in the third chapter. Descriptions of various entities that puzzle many ophthalmologists, such as subdural hematoma, are fully understandable.

The organization of the chapter on brain tumors is excellent. Each type of tumor is logically presented; the incidence, pathologic picture and prognosis are given, and a short clinical résumé is made. This results in easy understanding and retention of the essential characteristics of each of the many types of tumor that occur. The tumors that particularly concern the ophthalmologist, such as pituitary adenoma, suprasellar cyst, meningioma and angioma, are fully described, and their relations to the visual pathology are indicated. Cerebral abscess and hydrocephalus are discussed in the concluding chapters.

Although this book was written for the student of neurosurgery, it is of definite value to the neuro-ophthalmologist who needs a working knowledge of neurosurgical pathology. However, any ophthalmologist will be well repaid by even a few hours of study of this book.

P. J. LEINFELDER.

**Das Haftglas.** By Dr. E. Burki. Basel, Switzerland: S. Karger, 1948.

This book deals with the mathematical optics of contact glasses. The book is divided into two sections, a theoretic and a practical. The



latter is not so well developed as it might be and, since it is written in German, will not appeal to many practicing ophthalmologists. The theoretic section, on the other hand, is done with the usual German thoroughness. The book is recommended to those who are interested in the optics of contact glasses.

FRANCIS H. ADLER.

## LOCALIZING VALUE OF VISUAL FIELDS IN PATIENTS WITH EARLY CHIASMAL LESIONS

FRANCIS H. ADLER, M.D.

GEORGE AUSTIN, M.D.

AND

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PHILADELPHIA

THE MAJORITY of patients operated on for tumors in the neighborhood of the chiasm give a history of visual difficulty as their first noticeable complaint. In most cases the patient states that he noticed diminished vision of one eye coming on slowly, for which an oculist or an optometrist was consulted, and that numerous prescriptions for glasses were given without any benefit. The patient frequently states that he went from one eye specialist to another over a period of months, or even years, before some one finally took his visual fields and told him that something was pressing on his visual pathway and referred him to a neurosurgeon for diagnosis and treatment.

The history may also reveal that during this period the patient began to have headaches and various structural and physiologic abnormalities suggestive of pituitary dysfunction, but these symptoms are invariably not his chief complaint and are brought out only by careful questioning. Emphasis is nearly always laid on the disturbance in vision. This may be either a loss of central visual acuity or a noticeable contraction of half the visual field or both. The ophthalmologist is the one, therefore, who is directly responsible for the early diagnosis in these cases. The diagnosis can be made, or at least suggested, only by the changes in the visual fields. If peripheral fields alone are taken, the diagnosis will frequently be missed in the early stages, as only the central isopters show the earliest changes. Both central and peripheral isopters are necessary for the evaluation of the fields. Even with careful field studies, the diagnosis can be missed if one is not constantly alert to the fact that the fields may be atypical in the early stages and may not show characteristic signs of chiasmal interference, that is, bitemporal or homonymous hemianopsia.

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From the Departments of Ophthalmology and Neuro-Surgery of the Hospital of the University of Pennsylvania.

One of the patients reported on here (case 3) had a craniopharyngioma which was missed by one of us (F. H. A.), even though the fields were taken, because these studies showed only very early changes in the field of one eye when she was first examined.

In addition to their diagnostic value, visual fields taken early in the course of a chiasmal lesion should be of aid to the neurosurgeon in localizing the tumor in respect to the chiasm. Whenever possible, most neurosurgeons prefer to operate on the right side of the head for tumors in this neighborhood in order to avoid the speech center on the left side in right-handed people. This rule is broken, however, if the vision in one eye is very much worse than that in the other. In this case, it is preferred to make the approach on the side with the poorer vision. The roentgenographic findings may also help in the location of the lesion, but frequently they do not. It would be helpful to the surgeon if he could predict with reasonable accuracy on which side of the chiasm the tumor is situated—whether it is lateral, anterior or posterior, or whether it is coming directly up from below. It is reasonable to expect that some information could be derived from an analysis of the early field changes as to the direction from which a lesion is attacking the chiasm. Such information would also be suggestive of the nature of the lesion, that is, whether it is an intrasellar adenoma, a craniopharyngioma, a suprasellar meningioma or an aneurysm.

It is the experience of most authors that the late field changes have little localizing value. Traquair<sup>1</sup> stated:

Too much reliance should not be placed on the inferences from the field changes as to the exact site or position of a tumor or other lesion, though on the whole they may be regarded as a trustworthy guide to the point at which the nerve fibers are affected.

Many examples could be cited from the literature which demonstrate that one must be guarded against too positive a statement as to the localizing value of the fields. In speaking of the effects of pressure on the optic nerves themselves, for example, McConnell and Mooney<sup>2</sup> stated that loss of the lower nasal quadrants of the visual fields does not necessarily imply that the upper surfaces of the optic nerves are being pressed on. This has also been our experience (case 9). In several cases the optic nerves or tracts were found to be grooved by blood vessels at operation without any corresponding defects in the visual fields having been found prior to operation. On the other hand, a recent report of a case of suprasellar meningioma by Mathewson<sup>3</sup> indicates that in selected cases the early field changes may have definite

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1. Traquair, H. M.: *Introduction to Clinical Perimetry*, ed. 4, London, Henry Kimpton, 1942, p. 229.

2. McConnell, A. A., and Mooney, A. J.: *Brain* **61**:37, 1938.

3. Mathewson, W. R.: *Brit. J. Ophth.* **30**:92, 1946.

localizing value. Kestenbaum<sup>4</sup> reviewed the various types of chiasmal lesions and indicated the type of field change which should occur in lesions approaching the chiasm from different positions. We are not aware of any analysis having been made of a series of cases of verified chiasmal lesions for the purpose of determining how well one can predict the location of a lesion from the character of the early visual fields.

The present paper is a report of a series of cases in which the visual fields taken preoperatively were analyzed and the site of the tumor predicted on this basis alone, without knowledge of the operative findings. The theoretic location of the tumor was then compared with that described in the operative notes. All the cases are from the neurosurgical service of one of us (F. C. G.) in the Hospital of the University of Pennsylvania. Most of the fields were taken in the department of ophthalmology of the University Hospital. Only those cases were used in which the visual fields were taken early enough before operation to give a clue to the possible site of interference. In this way all cases were ruled out in which the defect had reached the stage of complete bitemporal hemianopsia. It should also be emphasized that all the cases were selected from the file of lesions around the chiasm. The interpretation of the fields was therefore made with the knowledge that the tumor was a chiasmal one.

The peculiar distribution of the nerve fibers in the chiasm should enable one to predict the situation of a growing tumor with some degree of accuracy, depending on where the tumor comes into contact with the chiasm. It is probable that the field changes are not due to direct pressure of the tumor on the nerve fibers, but depend rather on the shutting off of their blood supply, which causes an anoxia, preventing conduction in the fibers. This supposition is borne out by the rapidity with which the fields may return to normal after the pressure has been relieved by operation. It is common to find decided improvement, and even complete recovery, of the fields within several days of operation, a result which would not occur if the pressure had caused organic changes in the fibers.

Fibers from the upper half of each retina occupy the upper half of each optic nerve and run into the upper, or dorsal, part of the chiasm. Similarly, the fibers from the lower half of each retina are found in the lower half of each optic nerve and in the lower, or ventral, part of the chiasm. The chiasm can be thought of as made up of three layers of fibers: a lower, or most ventral; a middle, and, finally, an upper, or dorsal, layer. The uncrossed temporal fibers remain on the outside,

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4. Kestenbaum, A.: *Clinical Methods of Neuro-Ophthalmologic Examination*, New York, Grune & Stratton, Inc., 1947.

or temporal, surface of the chiasm. The fibers from each inferior temporal retinal quadrant run on the extreme outside, or lateral edge, of the chiasm and occupy the middle layer. The uncrossed fibers from each upper temporal retinal quadrant run nearer the midline and almost entirely in the upper, or dorsal, layer. The fibers from the inferior nasal retinal quadrant are found almost entirely in the lower, or most ventral, layer. These fibers lie in the anterior portion of the chiasm, and the most anterior of these swing forward into the opposite optic nerve to form the anterior knee. The fibers from the upper nasal retinal quadrant run backward almost into the optic tract on the same side before swinging across the chiasm into the opposite optic tract, skirting the posterior surface of the chiasm and eventually lying on the mesial side of the tract near its surface. They comprise the middle and uppermost layers of fibers. From this description, it is obvious that the lower layer of the chiasm is formed almost entirely of the crossing fibers from each inferior nasal retinal quadrant. These are the fibers which form the anterior knee in each optic nerve. The middle layer of the chiasm contains both crossing and noncrossing fibers, i. e., the crossing fibers from each superior nasal retinal quadrant and the noncrossing fibers from each superior temporal retinal quadrant. The upper layer is formed by both crossing and noncrossing fibers, i. e., those from the superior nasal retinal quadrant and the fibers from the superior temporal retinal quadrant. While this relationship may seem to be complex, Kestenbaum has considerably simplified it by pointing out that the result is, in general, what would be obtained by a rotation of the optic nerve around its anteroposterior axis 45 degrees toward each nasal side.

The macular fibers form a separate bundle throughout the chiasm, coming from the middle of the optic nerve as they enter the chiasm. The uncrossed temporal fibers go directly down the side of the chiasm, about equidistant from its lateral surface, to enter the tract on the same side at about its middle. The crossing macular fibers go to the posterior part of the chiasm before they cross to the opposite side, so that the actual crossing lies close to the posterior edge of the chiasm. In this situation they are in close vicinity to the third ventricle and, according to Kestenbaum, are separated from it only by Gudden's commissure. Figure 1 attempts to show the course of these fibers in a third dimensional drawing. The course of the fibers as outlined here is based largely on the work of Wilbrandt, and there has been little recent work of an anatomic nature which throws any further light on the arrangement of the fibers in the chiasm. Most of the evidence within recent years has come from an evaluation of clinical material. As Clark<sup>5</sup> pointed out,

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5. Clark, W. E. L.: *Physiol. Rev.* **22**:209, 1942.

The intimate topographical relation between the optic chiasma and certain hypothalamic commissures in this region makes it very difficult in normal preparations to decipher the precise course of the retinal fibres here. . . . For one thing, the fibres of the supra-optic commissures (which probably have nothing to do with visual functions) are not always distinguishable from retinal fibres. Also, in the chiasma the decussating fibres may run an aberrant course which can be very misleading to the casual observer.

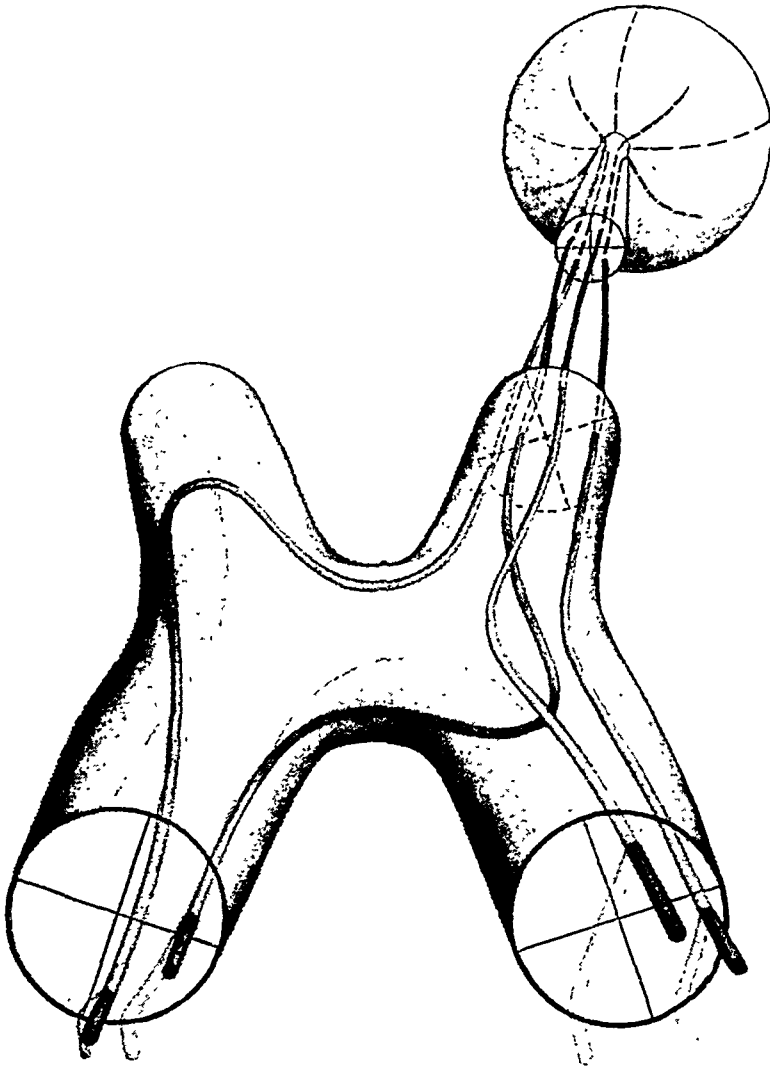


Fig. 1.—Arrangement of the fibers in the chiasm coming from the four quadrants of the retina as seen from the back of the eye.

1. The upper nasal quadrant of the retina sends fibers into the middle layer of the chiasm which form the posterior knee on the ipsilateral side before crossing over in the back of the chiasm.

2. The superior temporal quadrant sends fibers into the upper layer of the chiasm which form the portion of the uncrossed bundle nearest the midline.

3. The inferior temporal quadrant sends fibers into the middle layer of the chiasm which form the uncrossed bundle nearest the temporal surface of the chiasm.

4. The inferior nasal quadrant sends fibers in the lower layer of the chiasm which cross over at the anterior end of the chiasm to form the anterior knee.

## REPORT OF CASES

CASE 1.—R. C., aged 40, was admitted to the neurosurgical service on Sept. 5, 1947.

He had a history of failing vision in the right eye for months. He had consulted an ophthalmologist, who found a scotoma for red in the right visual field and told the patient to stop smoking, which he did, without any improvement. He had no headaches or other symptoms. His family physician finally referred him to one of us (F. C. G.).

On his admission, vision with best correction was 6/30 in the right eye and 6/7.5 in the left eye. His peripheral fields for 1/330 white and 6/330 red were practically full. There was a contraction of the upper temporal quadrant in the

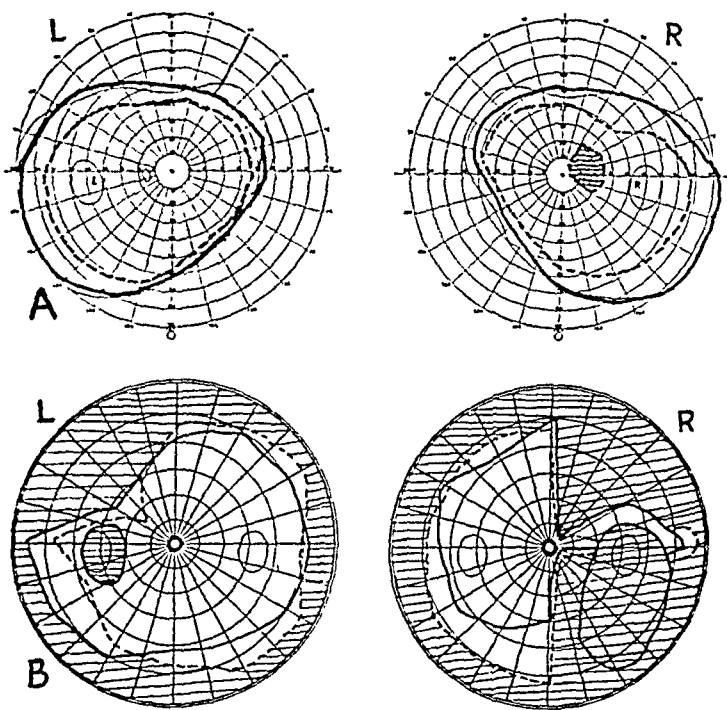


Fig. 2 (case 1).—*A*, peripheral fields to 1/330 white (solid line) and 5/330 red (broken line). The fields are full to 1/330 white. The right eye shows contraction of the upper temporal quadrant to 5/330 red and a scotoma to 5/330 red on the temporal side of fixation.

*B*, central fields, showing complete loss of the right temporal quadrant to 2/1,000 white and 10/1,000 red and loss of the left upper temporal quadrant to 2/1,000 white and 10/1,000 red.

right eye for 5/330 red and a scotoma for red on the temporal side of fixation in the right eye only. This was suggestive of a hemianopic scotoma. The central fields showed complete loss of the right temporal quadrant to 2/1,000 white and 10/1,000 red and loss of the left upper temporal quadrant to 2/1,000 white and 10/1,000 red (fig. 2 *A* and *B*).

An analysis of the fields placed the lesion under the anterior end of the chiasm on the right side, where the right optic nerve joins the chiasm (fig. 3).

*Operative Notes* (Dr. F. C. Grant).—"A right prefrontal craniotomy was performed. When the dura was opened, the right olfactory and right optic nerves

were seen, the latter humped up over a large, and what felt like a semicystic, tumor" (fig. 4).

The diagnosis was chromophobic adenoma of the pituitary gland.

*Comment.*—In this case the loss of the temporal field on the right side and of the upper temporal quadrant on the left side, together with loss of the crossing macular fibers on the right side, pointed to the location of the lesion and corresponded well with the situation found at operation.

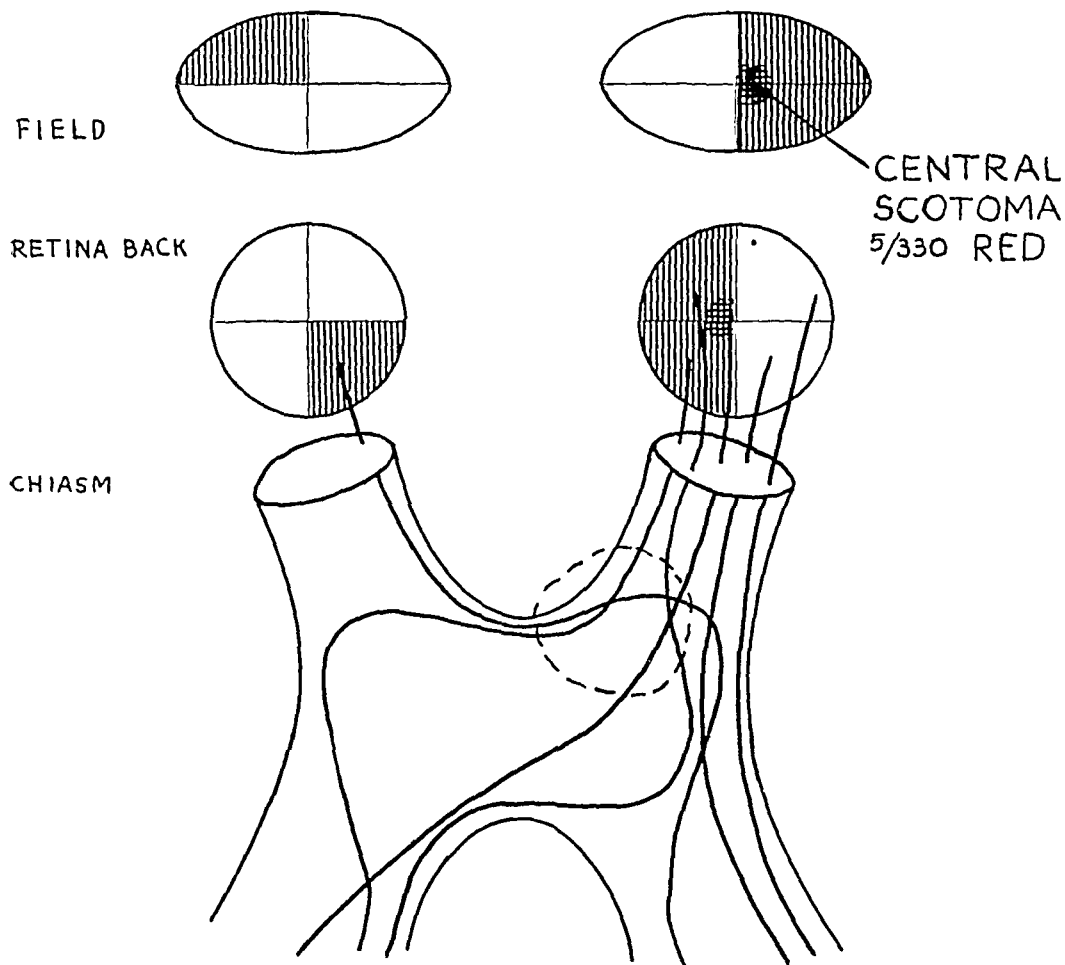


Fig. 3 (case 1).—Analysis of fields which placed the lesion under the front end of the chiasm on the right side where the right optic nerve joins the chiasm, catching fibers from the upper and lower nasal retinal quadrants on the right side and from the lower retinal quadrant on the left side.

CASE 2.—J. J., aged 36, was admitted to the neurosurgical service on March 22, 1943.

There was a history of poor vision for many years. He had been given numerous prescriptions for glasses by optometrists and ophthalmologists. One ophthalmologist found his disks pale and referred him to a neurologist, who gave him antisyphilitic treatment, despite a negative serologic reaction and a normal spinal fluid. He was then referred to the Wills Hospital, in 1940. At that time his peripheral fields showed a hemianopic scotoma to both white and color in the temporal half of each field. His visual acuity at that time was 6/10



in the right eye and 6/21 in the left eye with best correction. He was referred to Dr. Bernard Alpers for neurologic study, and a diagnosis of craniopharyngioma was made. He was eventually operated on (by Dr. Grant) on March 26, 1943.

Analysis of the early field changes of hemianopic central scotoma in each temporal field suggests a lesion pressing at the posterior end of the chiasm, catching the crossing macular fibers (fig. 5). From 1940 until operation, his fields showed an increasing loss of both upper and lower temporal quadrants until just prior to operation, when they showed a complete bitemporal hemianopsia to white, red and green.

*Operative Notes* (Dr. Grant).—"After a right transfrontal craniotomy, the dura was reflected from the right orbital plate and sectioned along the sphenoidal ridge.

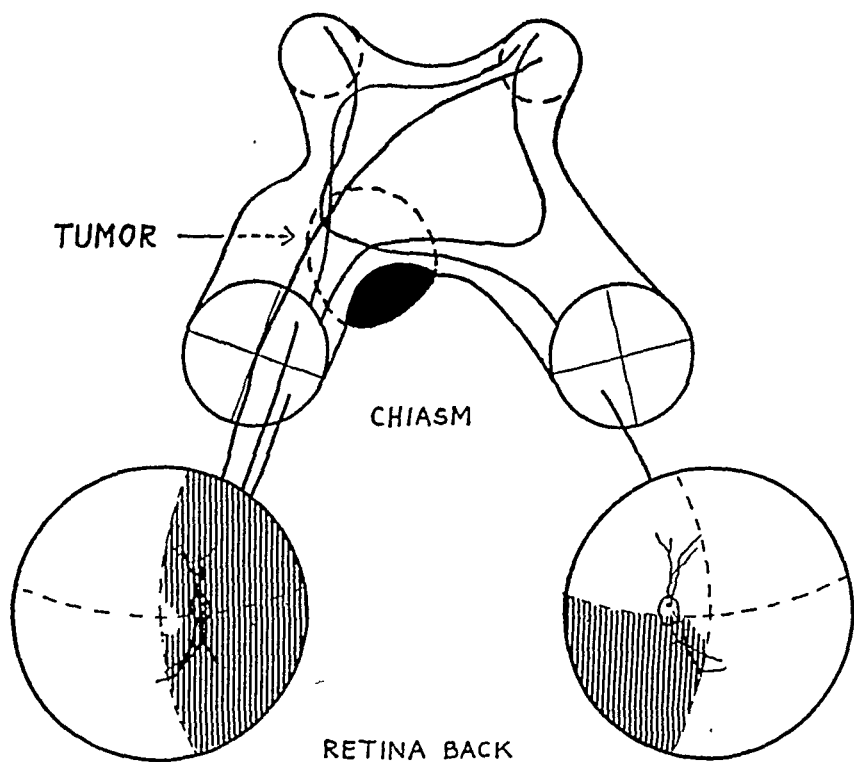


Fig. 4 (case 1).—Position of tumor found at operation under the front end of the chiasm on the right side.

This exposed the right optic nerve, which was tremendously distorted by a greenish tumor lying below and behind it. The tumor was thoroughly wrapped around the optic nerve and chiasm and extended well posteriorly. I thought I was able to see in front of the capsule into the sella, and possibly even to visualize the pituitary gland itself, lying in front of the anterior part of the tumor capsule."

The diagnosis was craniopharyngimatous cyst.

*Comment.*—In this case the bitemporal hemianopic scotoma suggested a lesion pressing at the posterior end of the chiasm and corresponded well to the situation of the tumor found at operation. It also was suggestive of the nature of the tumor, a craniopharyngioma.

CASE 3.—Mrs. W. C., aged 45, was admitted to the neurosurgical service on Nov. 21, 1941.

In June 1940 she complained of failure of vision in the left eye. She had consulted several ophthalmologists, who told her that they could find nothing wrong with her eyes. She was seen in the office of one of us (F. H. A.) in July 1940. Visual acuity was 6/7.5 in each eye. This could not be improved. Ophthalmoscopic examination revealed normal fundi. The patient seemed to be highly neurotic; she was told that nothing abnormal could be found and was asked to return. Visual fields were not taken at this time. She returned in January

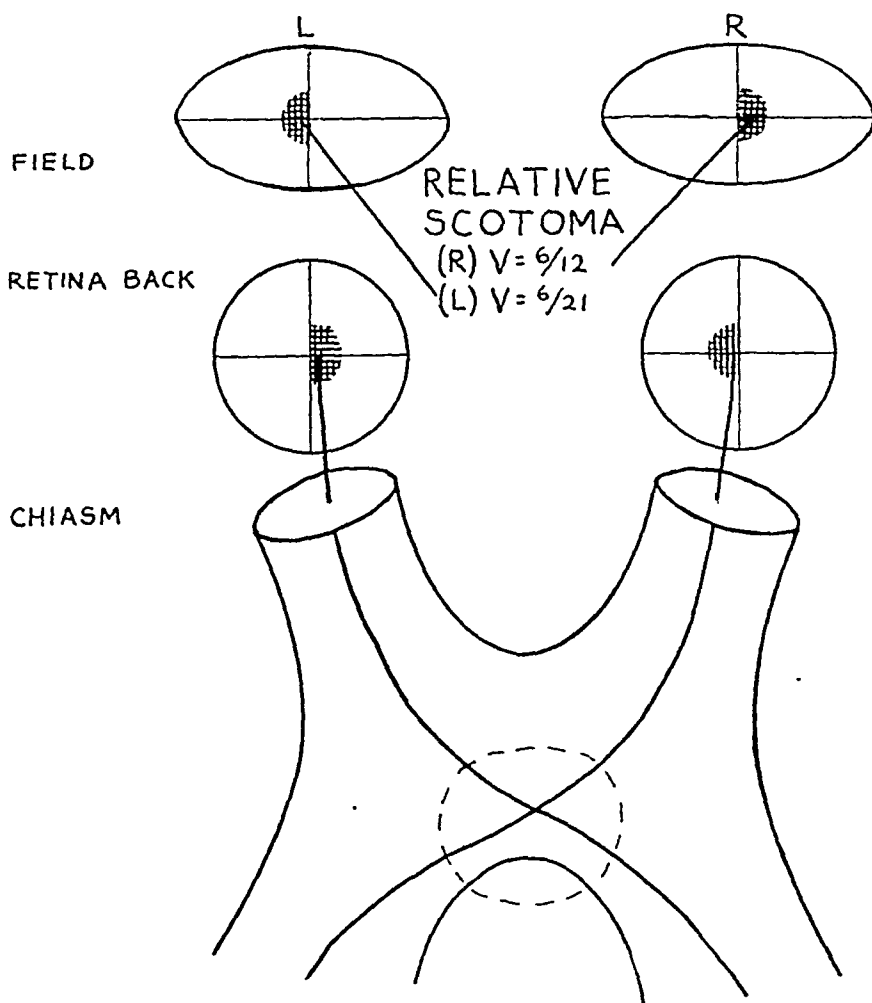


Fig. 5 (case 2).—Analysis of early changes in fields which showed a hemianopic central scotoma to 5/1,000 red. The position of the tumor was under the chiasm at the posterior end, catching crossing macular fibers.

1941, complaining of continued blurred vision in the left eye, which she said had become considerably worse. Her visual acuity was then 6/12 in the right eye and 6/150 in the left eye. This could not be improved with glasses. The fundi still showed no changes. Visual fields, which were then taken, showed a general contraction in the periphery of the right eye and approximately the same change in the left eye, but the loss was more marked in the upper temporal quadrant of the left eye. The central fields of the right eye were normal. The central fields of the left eye showed a slight cut in the upper temporal quadrant (fig. 6A). I wanted to use drops in her eyes and dilate her pupils, but she refused, saying

that her trouble had commenced when an ophthalmologist had put drops in her eyes. Accordingly, she left my office. The fields were not considered suggestive, and the cut in the upper temporal quadrant of the left eye was entirely overlooked. Nothing more was heard from her until she was reported as having entered Dr.

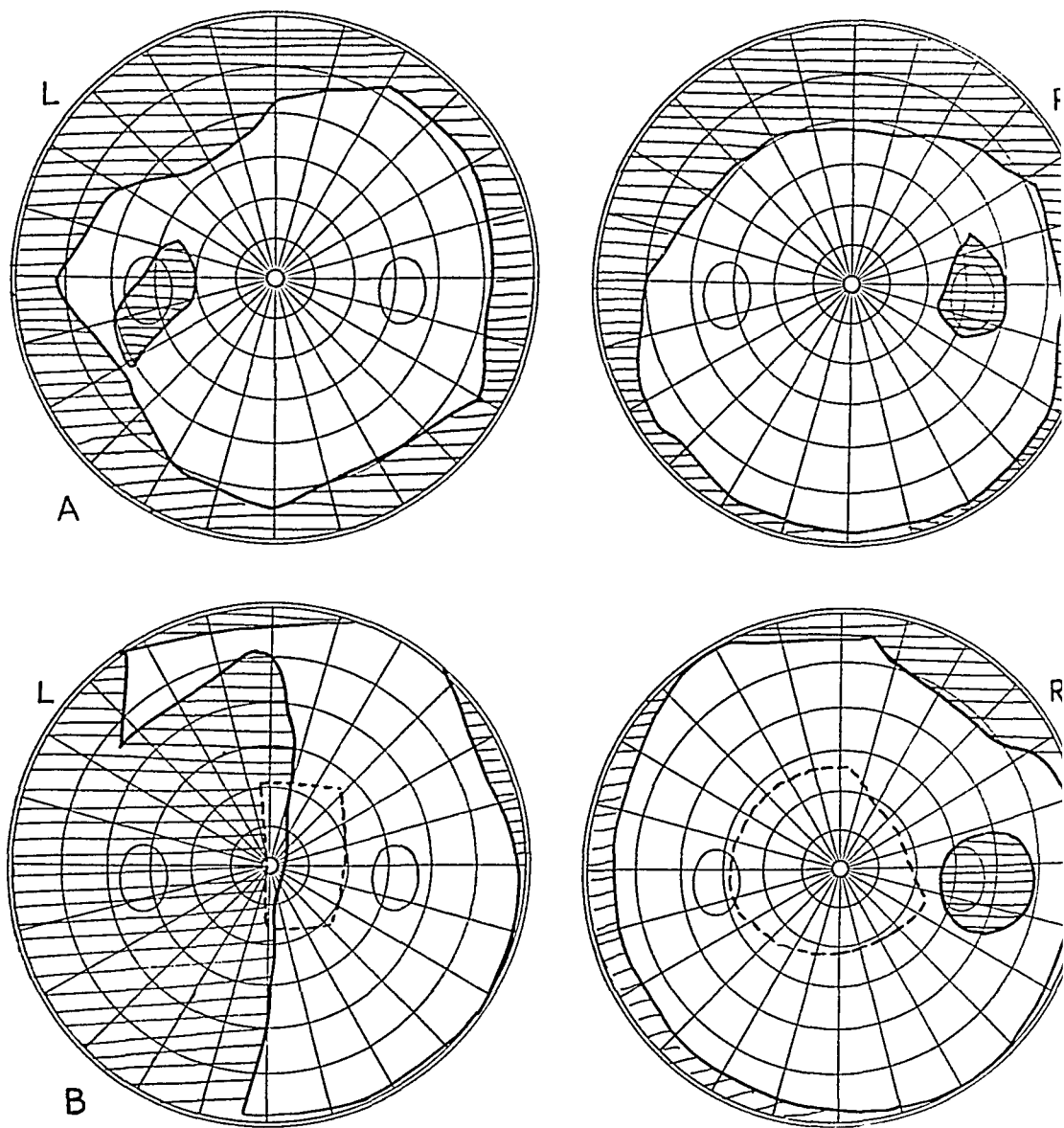


Fig. 6 (case 3).—*A*, central fields to 2/1,000 white, made on Jan. 24, 1941, showing cut in the upper temporal quadrant of the left field.

*B*, central fields to 1/1,000 white (solid line) and 3/1,000 red (broken line), made on Nov. 21, 1941, showing complete loss of the temporal field in the left eye and loss of the upper temporal quadrant in the right eye. Vision was 3/30 in the left eye and 6/12 in the right eye.

Grant's service on November 21, ten months later. She had been sent to Dr. Grant by another ophthalmologist, who two weeks previously had made a diagnosis of a tumor of the pituitary gland.

Fields which were taken in our outpatient department on Nov. 24 showed a definite upper temporal quadrant defect in the right eye and complete loss of the temporal field in the left eye (fig. 6B). Analysis of these fields indicates a tumor on the left side of the chiasm at its anterior part, catching both the upper and the lower nasal fibers of the left eye and the lower nasal fibers of the right eye (fig. 7). This case is similar to case 1 except that the tumor was on the opposite side.

*Operative Notes.*—"A left frontal craniotomy was performed. The dura was opened in the routine fashion and the left optic nerve exposed, revealing a tumor in the sella, which exerted pressure on the left optic nerve."

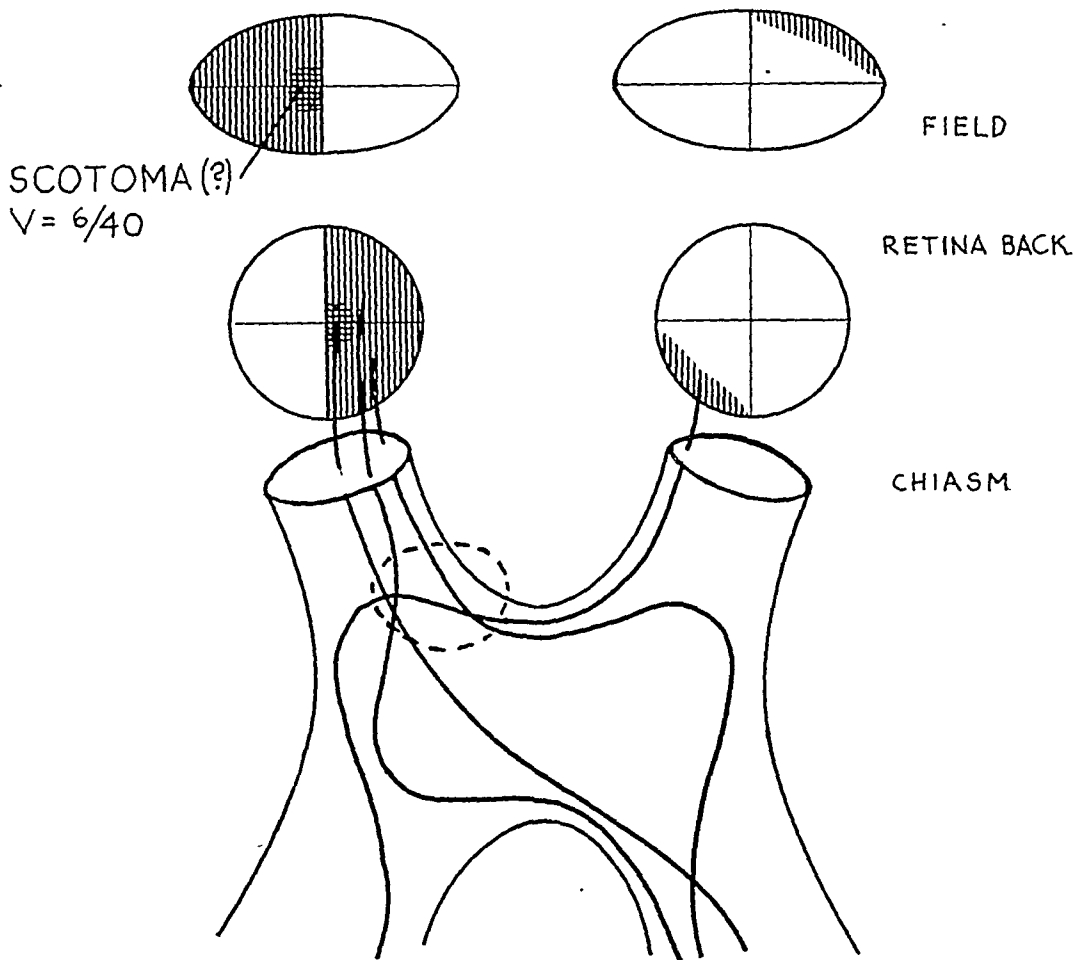


Fig. 7 (case 3).—Analysis of the fields, indicating a tumor on the left side of the chiasm underneath its anterior end, catching both the upper and the lower nasal fibers of the left eye and the lower nasal fibers of the right eye.

The diagnosis was eosinophilic adenoma of the pituitary gland.

*Comment.*—The diagnosis in this case was missed because of our failure to interpret the fields taken early in the course of the disease. It is certain that if the central fields had been taken with small colored test objects, characteristic fields would have been obtained. A year later the fields were unmistakable and localized the lesion in the place in which it was found at operation.

CASE 4.—K. B., aged 52, was admitted to the neurosurgical service on Sept. 17, 1947.

The patient had failing vision in the left eye for several years and glasses were changed repeatedly. In spite of this, her vision had continued to fail, and at the time of our examination her vision was very poor in the right eye

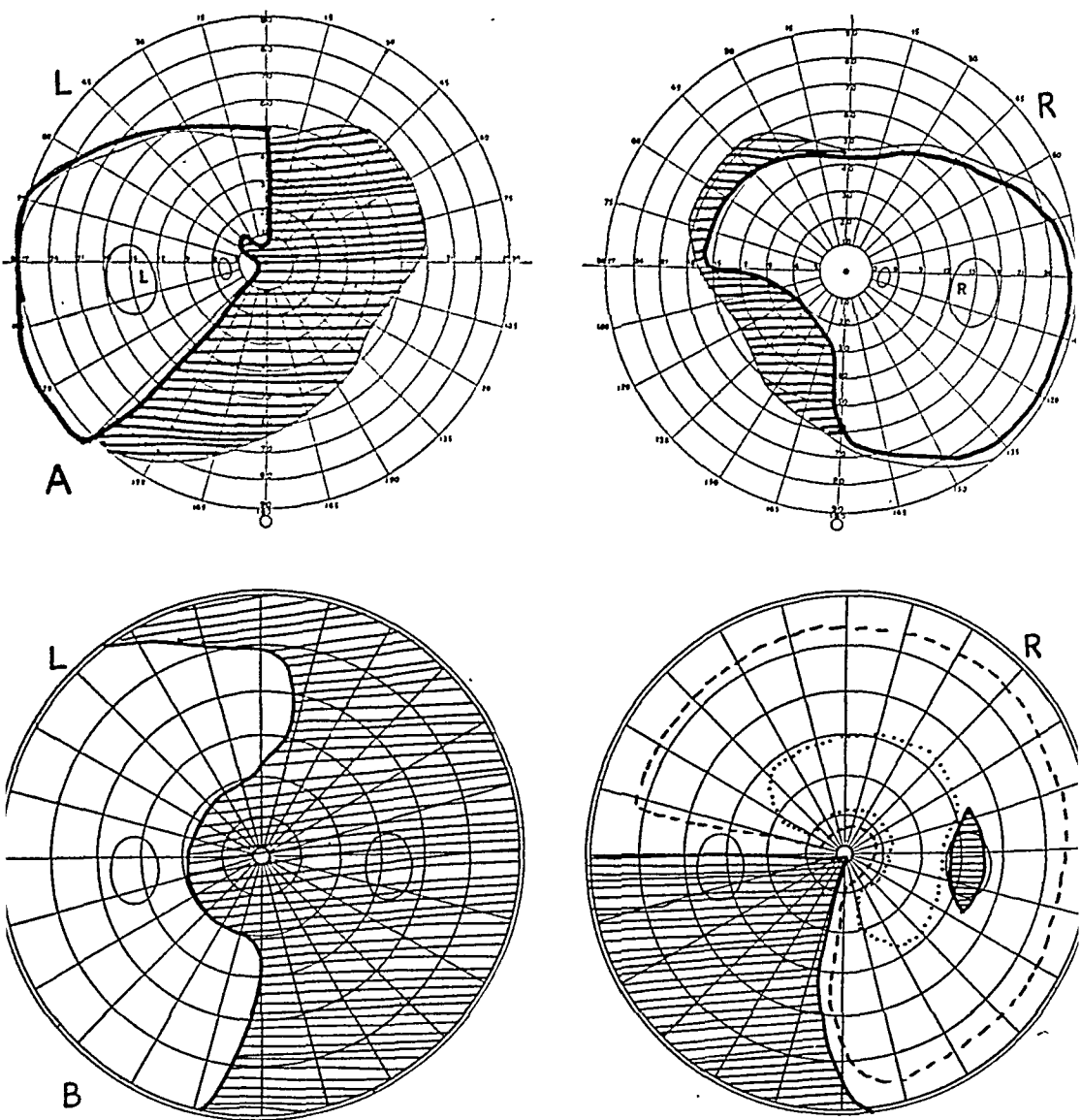


Fig. 8 (case 4).—*A*, peripheral fields to 10/330 white in the right eye and to 10/330 white in the left eye, made on Aug. 29, 1947.

*B*, central fields to 20/1,000 white (solid line), 5/1,000 white (broken line) and 3/1,000 white (dotted line), made on Aug. 29, 1947.

and practically gone in the left. She was seen two weeks prior to admission in our office by Dr. Harold G. Scheie. Her vision at that time was 6/120 in the right and was limited to hand movements in the left eye with best correction. Both optic nerve heads were pale, the left being more so than the right. Her

peripheral fields showed loss of the lower nasal quadrant in the right eye and complete loss of both nasal quadrants in the left eye, the defect extending into the lower temporal quadrant. Central fields bore this out along with the loss of the macular fibers in the left eye. Dr. Scheie made a diagnosis of bilateral primary optic nerve atrophy, more advanced in the left eye. He stated that because of the long history of loss of vision in the left eye, the most likely diagnosis was a neoplasm which caused the defect by direct pressure or by pressing the optic nerve laterally against the internal carotid arteries. He expressed the opinion that an aneurysm was possible and that basal arachnoiditis should be considered" (figs. 8 and 9).

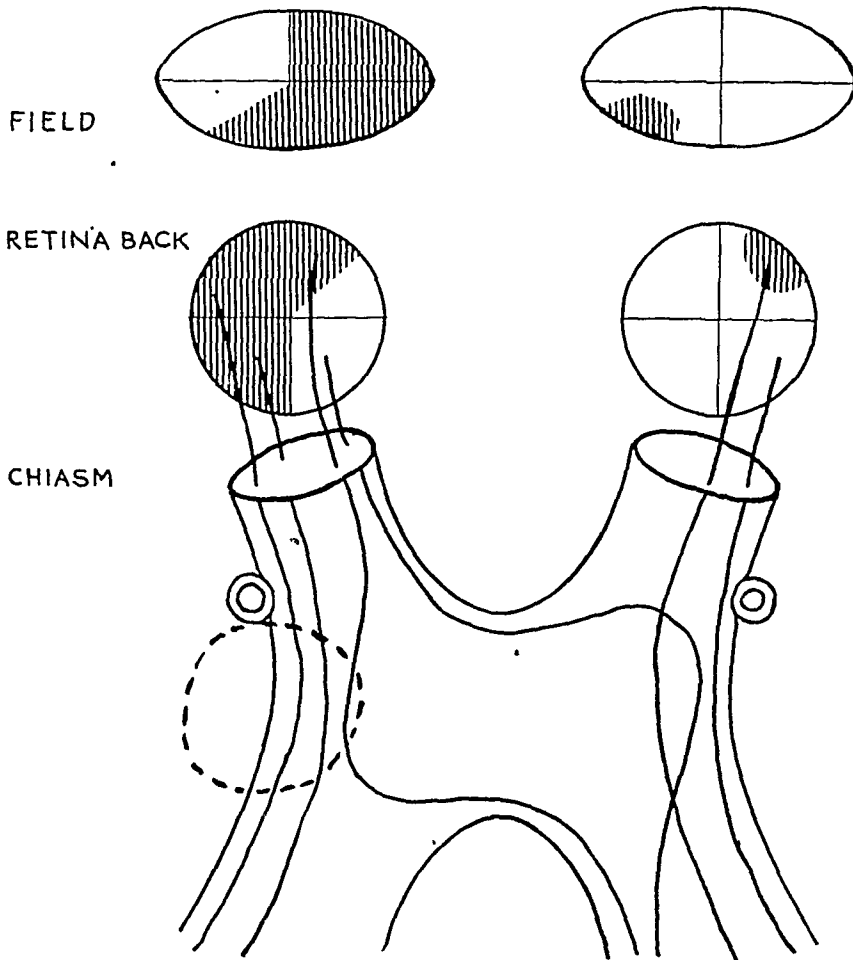


Fig. 9 (case 4).—Analysis of field defects indicating pressure on both sides of the chiasm in order to produce a binasal hemianopsia. The lesion is probably on the left side, pressing against the lateral aspect of the chiasm and pushing the chiasm over to the right, so that it presses against the right internal carotid artery or against the bony foramen. The fibers from the upper temporal quadrant on the right side, rather than those from the lower temporal quadrant, were pressed on. This may be due to the fact that the affected fibers lie in the upper part of the chiasm, where the artery comes in contact with the chiasm.

Analysis of the field defects indicates that pressure must have been present on both sides of the chiasm in order to produce binasal hemianopsia. The lesion was probably on the left side, pressing against the lateral aspect of the chiasm and pushing the chiasm over to the right, so that it pressed against the right internal carotid artery, or the right optic nerve pressed against the bony foramen.

The diagnosis was either a tumor or an aneurysm.

*Operative Notes* (Dr. Grant).—"A left frontal craniotomy was performed. A tumor was seen bulging well laterally to the left of the optic nerve, which had been stretched and thinned by the continuous pressure of the tumor, but which lay well within the lateral confines of the tumor. Gentle palpation of the tumor showed it to be cystic. It was thought that the lesion was probably a craniopharyngioma. In any event, before anything else was done, the cyst was needled and about 10 cc. of pure blood was obtained, with a fairly constant drip through the needle puncture wound. Suddenly, a violent hemorrhage broke from the aneurysm, seemingly central to and below it. It was necessary to amputate the entire left frontal lobe in order to control the bleeding. Clips were put on the left common carotid and the left internal carotid artery. Complete hemostasis was eventually secured, and, after a transfusion of 2 liters of blood, the patient left the table in fairly satisfactory condition. She never regained consciousness, however, and died the following day. Autopsy was not obtained."

The diagnosis was aneurysm of the left internal carotid artery.

*Comment.*—Although, in a recent paper, Igersheimer concluded that binasal hemianopsia is due to involvement of both optic nerves in front of the chiasm, the situation of the lesion in this case indicates that binasal hemianopsia may be produced by a lesion distinctly lateral to the chiasm. Unfortunately, in neither his case nor in ours was an autopsy obtained. Binasal hemianopsia is certainly suggestive of aneurysm, and such a lesion should be thought of at once in every case with such field defects.

CASE 5.—R. M., aged 50, was admitted to the neurosurgical service on Oct. 10, 1945.

There was a history of failing vision in the left eye for the past year. In February she was in an automobile accident; she ran into a car approaching from the right, which she did not see until it was directly in front of her. Vision was 6/15 and 6/60 on her admission. She was referred by Dr. George Meyer, who had made a diagnosis of intracranial tumor.

The fields showed loss of the upper temporal quadrant on the right side, extending into the lower temporal quadrant, and loss of the entire nasal half of the left field. Since it was known the tumor was a chiasmal one, our analysis indicated a tumor on the left side, impinging on the chiasm from the lateral aspect of its anterior end. Determination of the fields after admission showed a complete right homonymous hemianopsia, with more loss on the left side (fig. 10), indicating that fibers from the upper nasal quadrant of the right eye were now caught and implying that the tumor was progressing backward toward the left optic tract (fig. 11).

*Operative Notes* (Dr. Grant).—"Just lateral to the left optic nerve was encountered a reddish, fairly well encapsulated tumor, which lay lateral to the left optic nerve. It was obviously lateral to the pituitary fossa. It was finally coagulated, incised and a considerable piece removed with pituitary rongeurs for pathologic verification. It was then the impression that the tumor ran over in the midline and lay in the suprasellar position. The surgeon therefore threw back a right-sided flap in order to expose the right side as well. This was done without difficulty. The dura was much less adherent on this side, and one was able

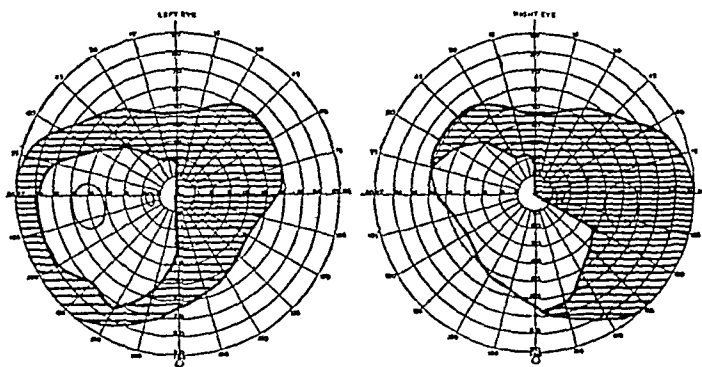


Fig. 10 (case 5).—Peripheral fields showing complete right homonymous hemianopsia, with more loss on the left side. Earlier fields showed a loss of the upper temporal quadrant alone on the right side. That the lower temporal quadrant on the right side is now being caught indicates that the fibers from the upper nasal quadrant of the right eye are being pressed on and implies that the tumor is progressing backward toward the left optic tract.

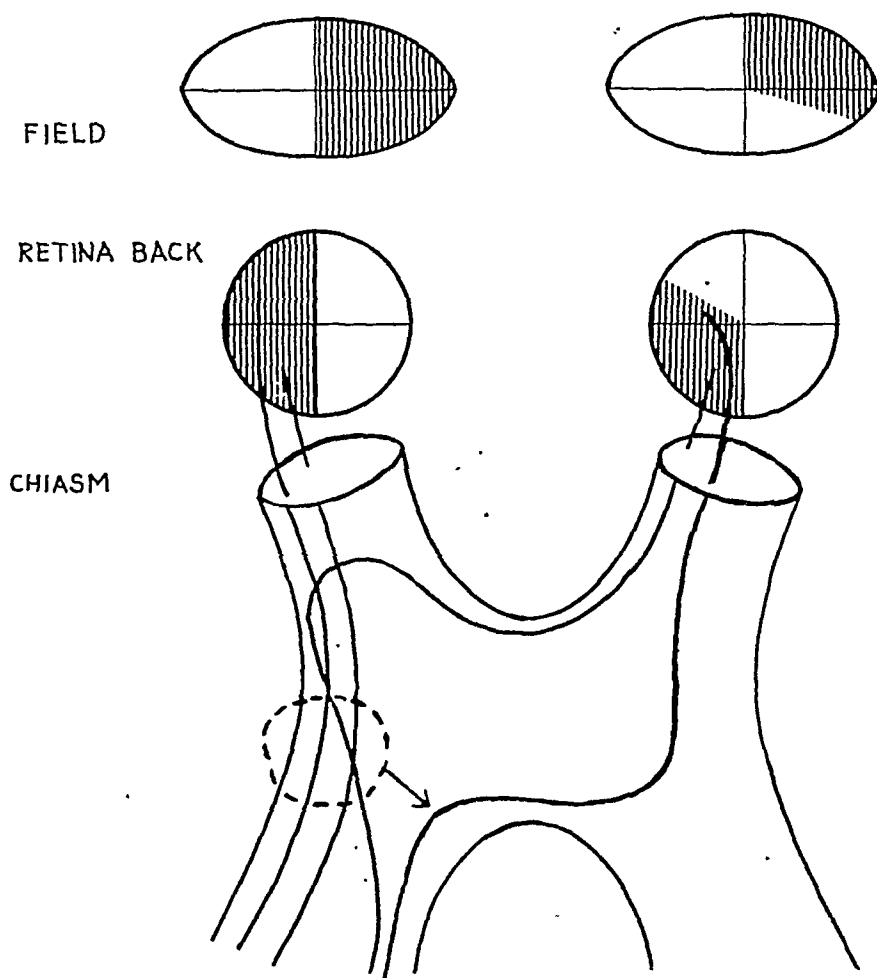


Fig. 11 (case 5).—Probable position of the tumor as indicated by the progression in the loss of the fields.



quite readily to see the right optic nerve, which did not seem to be involved by the tumor. The tumor seemed to lay lateral to, and just behind, the left optic nerve, probably involving the left optic tract."

The diagnosis was chromophobic adenoma of the pituitary gland.

*Comment.*—In this case, the early field defects, showing only loss of the upper temporal quadrant on the right side, indicated that the lesion was on the left side of the chiasm under the left optic nerve. As the lesion progressed, the lower temporal quadrant on the right side became affected, and this indicated that the tumor was growing backward, probably involving the left optic tract. The diagnosis was verified at operation.

CASE 6.—M. F., aged 16, was admitted to the neurosurgical service on Jan. 20, 1940.

There was a history of decreasing vision in the left eye since August 1939. Fields taken Jan. 5, 1940 at the Lewiston Hospital showed complete right homony-

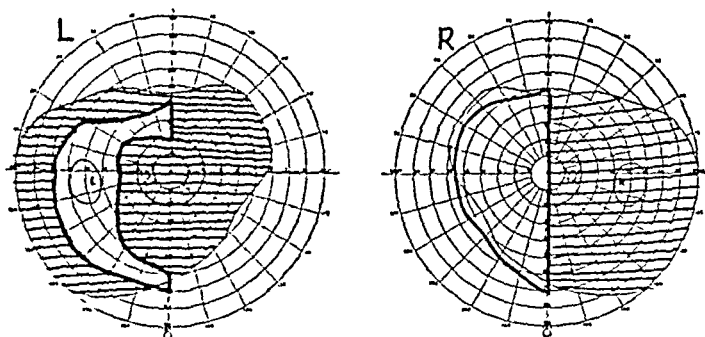


Fig. 12 (case 6).—Peripheral fields, showing loss of the right temporal field and total loss of the left nasal field with extension into the temporal quadrants as far as 30 degrees from fixation and complete loss of the left temporal crescent, leaving an island of vision.

mous hemianopsia with loss of central vision in the left eye. The eyes were otherwise normal. The diagnosis was tumor of the left temporal region.

On her admission, the fields (fig. 12) showed total loss of the temporal field in the right eye and a total loss of the nasal field in the left eye. The loss in this field extended over fixation into the temporal field to 30 degrees in the horizontal. There was also complete loss of the temporal crescent, leaving an island of vision. The fields were difficult to analyze. The defect in the center of the left field was too large for a central scotoma. The seeing temporal area was too large for a so-called temporal island. Loss of extreme temporal rim might be interpreted as loss of the temporal crescent belonging to the uniocular field, but there is no place in the chiasm where these fibers alone can be picked out. According to Traquair, the lesion should be back in the left optic tract, with pressure exerted on the tract from the mesial aspect (fig. 13).

*Operative Notes.*—"Between the left optic nerve and the left internal carotid artery, there presented a calcified artery and a dark green, shiny membrane, which was obviously part of a cyst."

The diagnosis was adamantinoma.

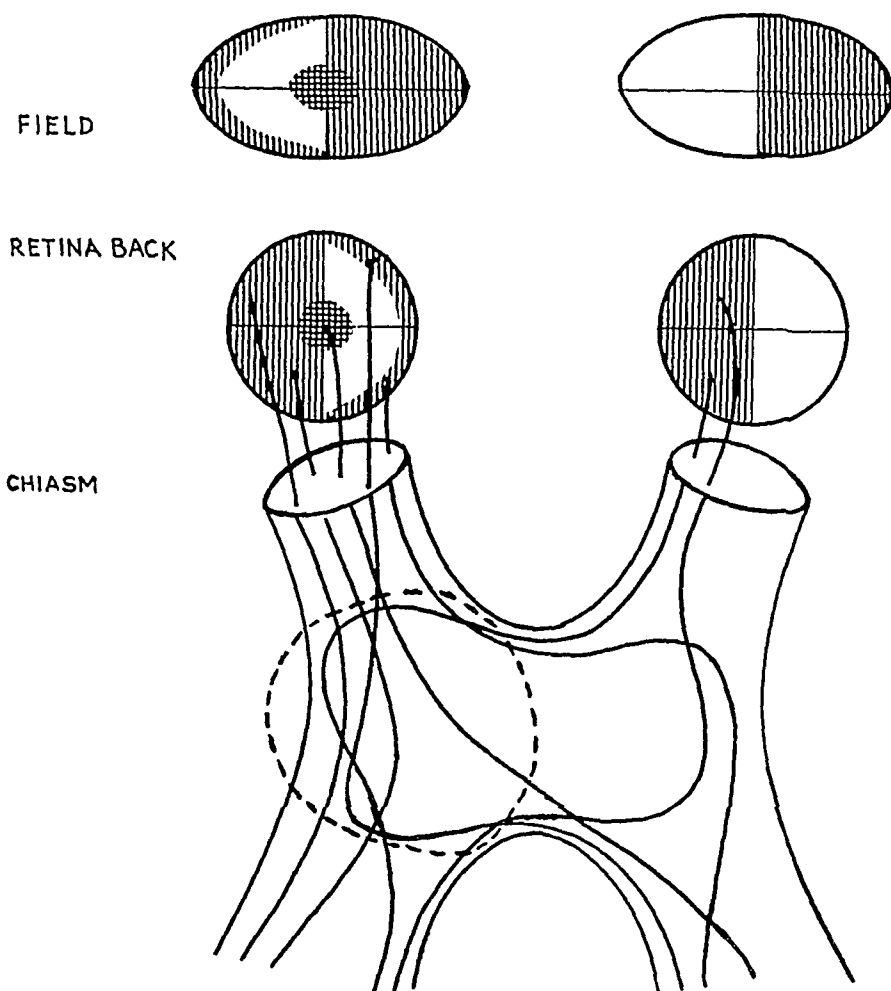


Fig. 13 (case 6).—According to Traquair, the lesion should be back in the left optic tract with pressure exerted on the tract from the mesial aspect.

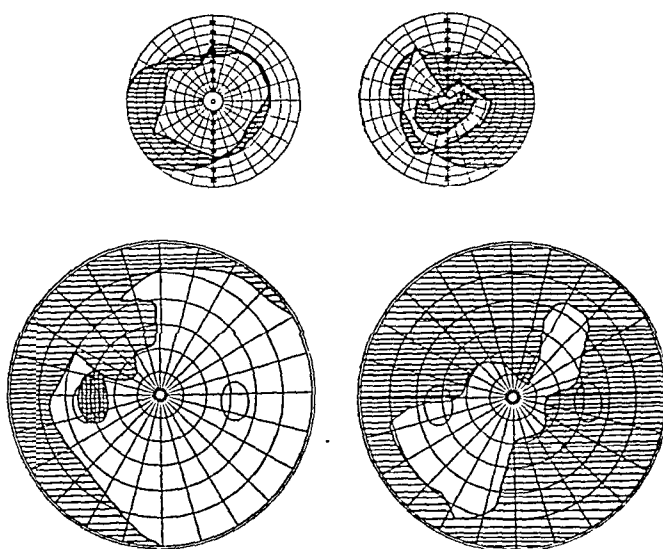


Fig. 14 (case 7).—Peripheral and central fields, showing partial loss of upper and lower temporal quadrants on the right side, with a nerve fiber bundle defect running from the blindspot below fixation to end on the horizontal raphe on the nasal side, and beginning loss of the temporal field in the left eye, more marked in the upper quadrant.

*Comment.*—In this case, an analysis of the changes in the fields did not agree with the position of the lesion as actually found at operation.

CASE 7.—T. M., aged 46, complained of loss of vision in the right eye and was referred to us by an optometrist, who suspected a chiasmal lesion. The visual field in the right eye was complex. There were partial loss of both temporal quadrants and a nerve fiber bundle defect running from the blindspot below fixation and ending on the horizontal raphe on the nasal half of the field. The left eye showed beginning loss of the upper temporal field and some loss of the lower temporal field (fig. 14). Analysis of the field placed the lesion in the

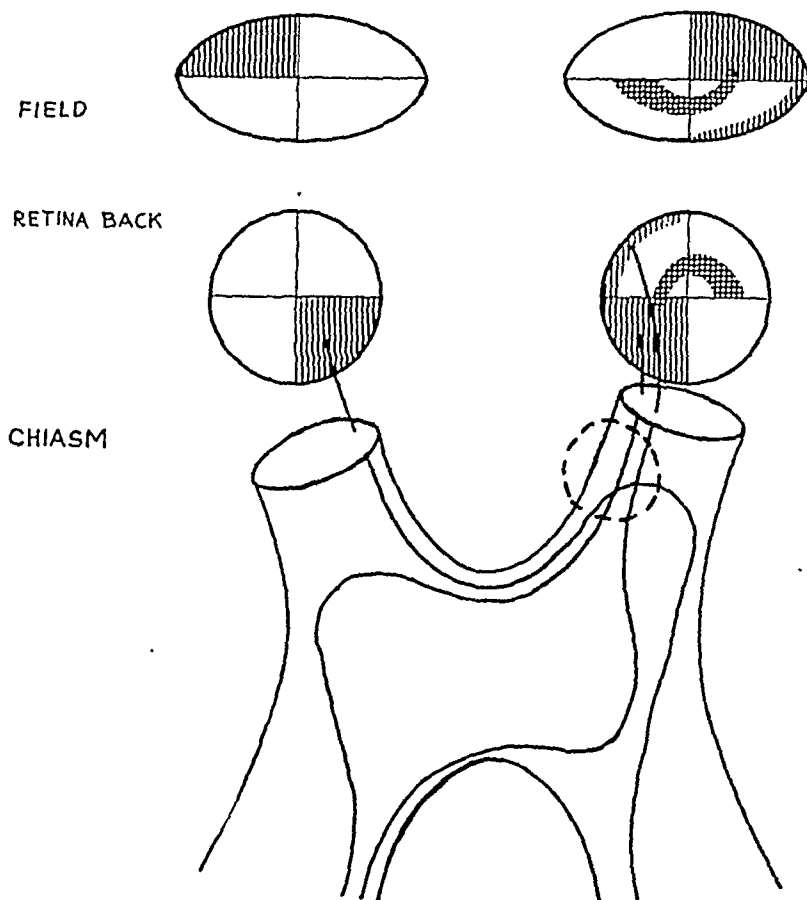


Fig. 15 (case 7).—Analysis of the fields indicating a tumor under the chiasm on the right side, involving the right optic nerve as well.

right optic nerve, well forward, and probably involving blood vessels of the nerve itself, with production of the nerve fiber bundle defect (fig. 15). Such scotomas are not uncommon with vascular lesions in the nerve. Vision was limited to hand movements in the right eye and was 6/12 in the left eye. Neither eye showed any optic nerve atrophy.

*Operative Notes.*—"The right optic nerve was humped over a tumor, the spur of which had almost penetrated the center of the nerve. There was a bluish tumor in the fossa. The tumor was needled and no fluid was obtained."

The diagnosis was cystic chromophobit adenoma.

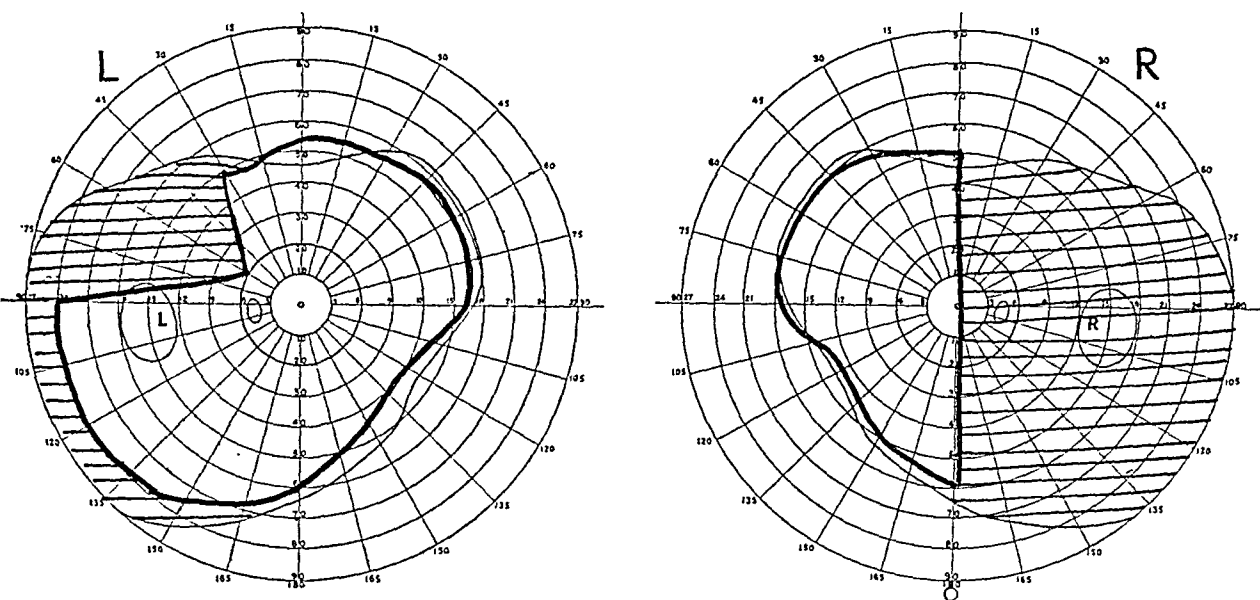


Fig. 16 (case 8).—Peripheral fields to 1/330 white, made on Nov. 25, 1946, showing complete loss of the temporal quadrants in the right eye and loss of the upper temporal quadrant in the left eye. Vision was 20/20 in the left eye and 20/70 in the right eye.

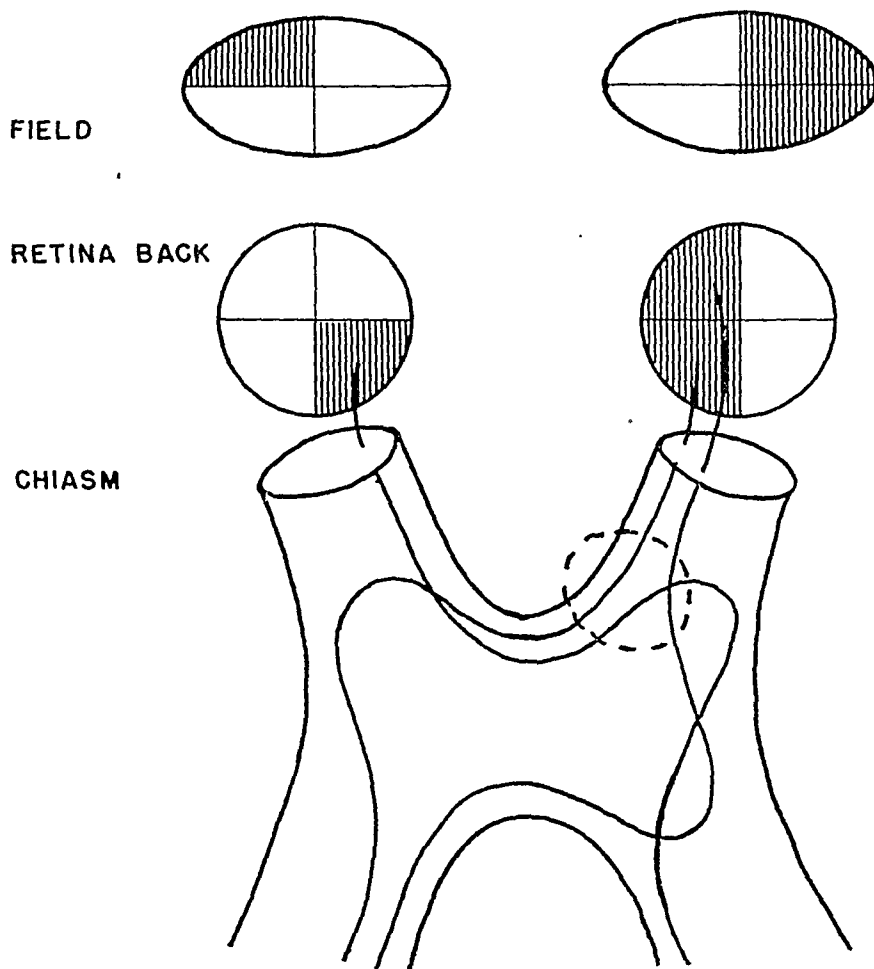


Fig. 17 (case 8).—Analysis of fields indicating a tumor under the anterior end of the chiasm.

*Comment.*—In a case of bitemporal hemianopsia, cecocentral scotomas, nerve fiber bundle defects or horizontal hemianopic defects should suggest involvement of the nerve on the side of the defect. The analysis of the position of the tumor in this case corresponded well with that found at operation.

**CASE 8.**—A. di S., aged 32, was admitted to the neurosurgical service on Nov. 24, 1946. Five months previously, at a routine examination for change of glasses, it was found that he had a right temporal field cut. The patient's brother, who was a physician, advised investigation. Fields taken the day after admission showed complete loss of the temporal field of the right eye and loss of the upper temporal quadrant of the left eye (fig. 16). Visual acuity was 20/70 and 20/20, respectively. The patient had definite acromegaly, and roentgenograms showed enormous enlargement of the hypophysial fossa. The diagnosis was an intrasellar lesion with a slight parasellar extension on the right side.

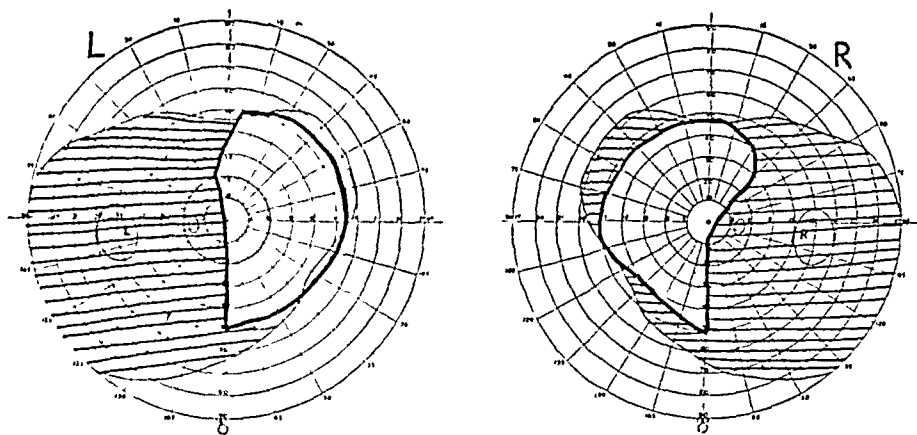


Fig. 18 (case 9).—Peripheral fields to 1/330 white, made on Dec. 7, 1945, showing almost complete bitemporal hemianopsia with some sparing of the upper temporal quadrant on the right side.

The visual fields taken prior to the patient's admission were similar to those taken in the hospital. Analysis of the fields indicated a tumor at the anterior end of the chiasm under the right optic nerve (fig. 17).

*Operative Notes.*—"Right frontal flap was formed. The right optic nerve was found moderately distended over a bluish, purplish tumor which lay in the sella."

The diagnosis was adenoma of the pituitary gland, predominantly eosinophilic.

**CASE 9.**—T. H., aged 37, was admitted to the neurosurgical service on Dec. 7, 1945.

*History.*—The patient had blurred vision in the right eye for three months. She was not helped by change of glasses. Six weeks previously she had noticed that she was not able to see in the temporal half of the right visual field.

Fields made on her admission showed almost complete bitemporal hemianopsia (fig. 18). The upper temporal quadrant of the right field, however, was more spared than the lower temporal quadrant, indicating that the fibers from the lower nasal portion of the retina on the right side were not so much involved

as the fibers from the upper nasal portion of the retina. The fibers from the lower nasal part of the retina are the ones which cross over in the front of the chiasm into the left optic nerve, forming the knee. It would appear, therefore, that the tumor was probably somewhat posterior and a little to the right side, but the fields have little localizing value. Since her vision in the right eye was limited to counting fingers and to 6/22 in the left eye, it was probable that the macular fibers on the right side were also involved (fig. 19).

*Operative Notes.*—"From the standpoint of physiology and visual fields the diagnosis was a definite lesion of the pituitary gland. The roentgenogram, how-

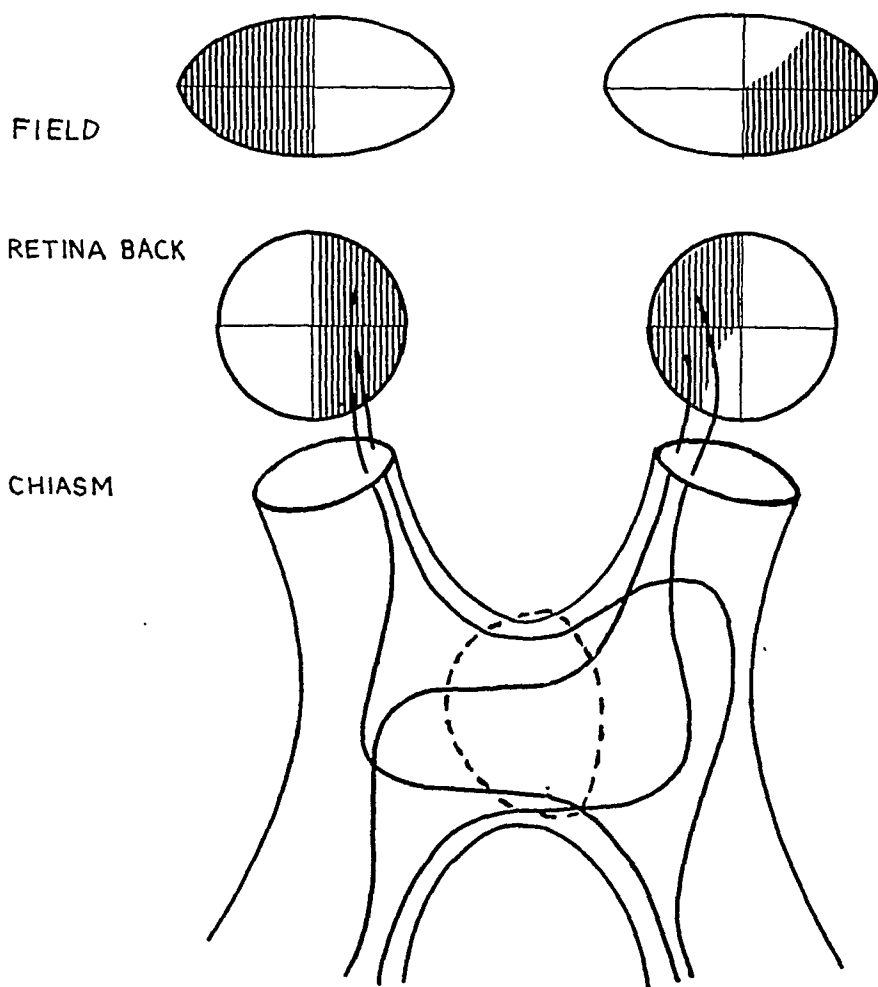


Fig. 19 (case 9).—Analysis of the fields indicating that the fibers from the lower nasal retina on the right side were not so much involved as the fibers from the upper nasal retina. This would indicate that the tumor was somewhat posterior and a little at the right side of the midline.

ever, showed little or no change in the pituitary fossa. The visual acuity on the right side was poorer than on the left, so that the operative approach was from the right side. The orbital plate was exposed and the dura incised along the sphenoidal ridge. This exposed the right optic nerve and the optic chiasm, which was obviously humped upward and forward over a neoplasm. The neoplasm, however, lay more posterior than usual, and its anterior surface could just be glimpsed between the optic nerves. There was a definite furrow in the right optic tract caused by pressure of the right anterior cerebral vessel."

## SUMMARY

Nine cases are reported of lesions in the neighborhood of the chiasm which indicate that some information as to the position of the lesion in respect to the chiasm may be gained by an analysis of the early field changes. The visual fields in these cases were such as to suggest the location of chiasmal interference, and after this had been predicated, a comparison was made with the findings at operation. It should be noted that in all these cases it was known that the lesion was in the neighborhood of the chiasm and that only those cases were selected in which the changes in the fields gave some suggestion of the site of interference. Even with these advantages, the localization in several cases was somewhat inaccurate. It would appear, therefore, that in selected cases the early fields are of definite, but not absolute, value in localizing the site of the lesion. The following changes have the greatest localizing value:

1. Bitemporal hemianopic scotoma with or without bitemporal contraction suggests a lesion encroaching on the posterior surface of the chiasm. Typical bitemporal defects may not appear until later. These fields are suggestive of craniopharyngiomas.

2. Loss of one temporal field with loss of the opposite superior temporal quadrant suggests a tumor lying on the side of the greater field loss at the anterior end of the chiasm under the optic nerve. When this picture is followed by loss of the lower temporal field on the side with the quadrant defect, the lesion is probably coming up through the chiasm. These fields seem to be characteristic of adenomas of the pituitary gland.

3. Binasal hemianopsia with one side more complete than the other, especially if extending into the temporal field on that side, indicates pressure at the lateral aspects of the chiasm on both sides. The lesion probably lies on the side with the greater field loss, and the opposite field defect is due to pressure of the opposite internal carotid artery or to pressure of the lateral aspect of the nerve against the bony optic foramen.

4. Bitemporal hemianopic fields with bizarre scotomas, cecocentral, altitudinal or in the nature of nerve fiber bundle defects, indicate a tumor at the anterior end of the chiasm, probably involving the nerve on the side of the scotoma.

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# THE CORNEA

## I. Swelling Properties of the Fibrous Tunic of the Eye

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AND

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THE CORNEA is the most important refractive surface in the eyes of animals living in air. This often overlooked fact places the cornea second only to the retina in importance of the ocular tissues to visual function, for without this effect of the cornea no proper retinal image could be formed. In order for light to reach the retina, it is vital of course that the cornea remain transparent. Opacities of the cornea present a real problem in practical therapeutics and have led, therefore, to a consideration of why the cornea is transparent in the first place, what if anything can be done about opacities of the cornea and why the sclera is not transparent, since it is structurally homologous to the cornea.

In outlining an experimental approach to these questions, we have a number of well known observations to guide us. In the first place, it was pointed out by Walls<sup>1</sup> that cornea and sclera are both transparent in early embryonic development and that in many of the lower animals the sclera of the adult eye is almost as transparent as the cornea. Since the entire fibrous tunic is transparent from the start, perhaps one should ask why the sclera is opaque rather than why the cornea is transparent.

The next observation of importance lies in the histology of the fibrous tunic. The sclera is composed of long collagenous fibers of unknown length felted together very closely. In the cornea, the lamellas are compact but much less felted than in the sclera, and the fibers are parallel and in definite layers. It is well known that pressure on the intact eye produces clouding of the cornea, which disappears again on release of the pressure. Insertion of a needle into the cornea

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Supported in part by a grant from the John and Mary R. Markle Foundation.

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1. Walls, G.: *The Vertebrate Eye and Its Adaptive Radiation*, Bloomfield Hills, Mich., Cranbrook Institute of Science, 1942.



leaves an opaque spot, which persists for a prolonged period. These simple and well known observations lead one to expect to find mechanical, as well as chemical, factors in the transmission of light by the fibrous tunic of the eye.

In consideration of the purely chemical factors in this problem, one is reminded that the fibrous tunic is composed of collagenous fibers which on boiling yield gelatin. Extensive chemical studies have been made in years past on tissues of this type, especially on the derived product, gelatin.<sup>2</sup> Therefore, there is much to guide one in previous work, and comparisons should be helpful. It should be pointed out, however, that transmission of light is the dominant consideration in the study of the eye, whereas with other protein systems interest in optical properties has been a minor issue.

The most characteristic feature of the fibrous tunic, *in vitro*, is that it tends to imbibe fluid in aqueous solutions. Cogan and Kinsey<sup>3</sup> emphasized the water content of the cornea as the chief determining factor in transparency of this tissue, and as the one responsible for the optical difference between cornea and sclera. The first paper of our series, therefore, constitutes a study of the swelling properties of the fibrous tunic. In this paper we show that, although the cornea and the sclera are both composed of collagenous fibers, there is a decided structural difference between the two tissues, as brought out by the striking differences in swelling behavior. These differences in swelling were predicted from what is known of the arrangement of the collagenous fibers from histologic studies, as previously noted. The importance of this structural difference becomes apparent in the second paper, in which we study the factors affecting the transmission of visible light by the cornea and sclera.

#### METHODS AND MATERIAL

Whole eyes were removed from freshly killed cattle and transported to the laboratory in tap water. The cornea was removed by making a primary incision with a cataract knife and cutting around the corneo-scleral junction with iris scissors so as not to include the scleral spur. The epithelium was peeled off early in each experiment.

All observations on swelling were made in buffered solutions of varying composition and hydrogen ion concentration, and all solutions

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2. Schmidt, C. L. A.: *Chemistry of the Amino Acids and Proteins*, Springfield, Ill., Charles C Thomas, Publisher, 1938.

3. Kinsey, V. E., and Cogan, D. G.: The Cornea: III. Hydration Properties of Excised Corneal Pieces, *Arch. Ophth.* **28**:272-284 (Aug.) 1942; IV. Hydration Properties of the Whole Cornea, *ibid.* **28**:449-463 (Sept.) 1942; V. Physiologic Aspects, *ibid.* **28**:661-669 (Oct.) 1942; *Physiologic Studies on the Cornea*, *Science* **95**:607-608, 1942.

were adjusted to the same osmotic activity. Although we found, as did Cogan and Kinsey, that adjustment to isosmotic activity did not greatly alter the general results in this study, we present our methods for preparing such solutions, for the benefit of those who have occasion to make similar observations.

Acetate buffer of 0.2 normal strength was chosen because the osmotic activity of the buffer mixture at  $p_H$  5.6 is 9.00 atmospheres, a figure which lies between the values for the two solutions normally bathing the respective surfaces of the cornea. All other buffers of the acetate series were brought to the same osmotic activity by adding dextrose. Buffers made from other ingredients were likewise brought to 9.00 atmospheres by adding dextrose. All solutions were checked with depressions of the freezing point, and the  $p_H$  was determined with the glass electrode at room temperature. A simplified technic of calculation was used, which may be applied to any solution. Suitable constants for simplifying calculation were arrived at in the following manner:

Total osmotic activity is given by the equation

$$OP = \frac{N}{V} RT \phi$$

in which  $OP$  is osmotic pressure, in atmospheres,  $N$  is the number of moles of solute per liter,  $V$  is the volume of solution,  $R$  is the gas constant (0.082 liter atmosphere per degree per mole),  $T$  is the absolute temperature and  $\phi$  is the osmotic coefficient.

Sodium acetate:

$$1 \text{ cc. } 0.2 \text{ normal (N) sodium acetate (NaAc)} = 0.0164 \text{ Gm.}$$

$$N = \frac{\text{Cc. } 0.2 \text{ N NaAc/L.} \times 0.0164}{\text{Molecular weight of NaAc}} \times 2 \text{ (for ionization)}$$

$$\text{At } 0.2 \text{ N: } \frac{\Delta t^4}{N} = 3.58 \text{ C.; } \phi = \frac{3.58}{1.86 \times 2} = 0.962$$

$$\int_{\text{NaAc}} = 0.962 \times \frac{0.0164}{82} \times 2 \times 0.082 \times 298 = 0.0094^5 \text{ atmosphere/cc. NaAc/L.}$$

$$OP_{\text{NaAc}} = \int_{\text{NaAc}} \times (\text{number cc. } 0.2 \text{ N NaAc added per liter})$$

- 
4.  $\Delta t$  equals lowering of freezing point, expressed in degrees Centigrade.  
 $\frac{\Delta t}{N}$  equals lowering of molar freezing point.

5. To justify the use of 2 twice here:  $3.58/1.86$  would represent the osmotic activity of one molecule of sodium acetate, just as  $3.58/(1.86 \times 2)$  indicates the osmotic activity of one particle (i. e., one ion) of sodium acetate. In other words,  $3.58/1.86$  is the molecular osmotic coefficient ( $\phi$ ), while  $3.58/(1.86 \times 2)$  is the particular, or ionic, coefficient ( $\phi$ ). Thus, if the ionic coefficient is used, one must multiply the number of moles ( $N$ ) of sodium acetate or acetic acid used by 2 in order to take dissociation into account.

Acetic acid:

$$1 \text{ cc. } 0.2 \text{ normal (N) acetic acid (HAc)} = 0.012 \text{ Gm.}$$

$$N = \frac{\text{Cc. } 0.2 \text{ N HAc} / \text{L.} \times 0.012}{\text{Molecular weight of HAc}} \times 2 \text{ for ionization}$$

$$\text{At } 0.2 \text{ N: } \frac{\Delta t}{N} = 1.88 \text{ C.; } \phi = \frac{1.88}{1.86 \times 2} = 0.506$$

$$\int_{\text{HAc}} = 0.506 \times \frac{0.012}{60} \times 2 \times 0.082 \times 298 = 0.00495 \text{ atmosphere} / \text{cc. HAc} / \text{L.}$$

$$OP_{\text{HAc}} = \int_{\text{HAc}} \times (\text{number cc. } 0.2 \text{ N HAc added per liter})$$

Dextrose:

$$OP = \phi \frac{N}{V} RT; N = \frac{OP \times V}{\phi RT}$$

$$\frac{1}{(1.01) (0.082) (298)} \times 180 \times \frac{100}{1,000} = 0.727 \text{ Gm. of dextrose} / 100 \text{ cc. for 1 atmosphere}$$

$$\text{Grams dextrose desired at } p_H X = (\text{desired } OP - OP_{\text{NaAc}} - OP_{\text{HAc}}) \times 0.727$$

Sample calculation:

$$OP_{\text{NaAc}_{6.6}} = 0.0094 \times 910 = 8.55 \text{ atmospheres}$$

$$OP_{\text{HAc}_{6.6}} = 0.00495 \times 90 = 0.45 \text{ atmosphere}$$

$$\text{Total } OP_{6.6} = 9.00 \text{ atmospheres}$$

$$OP_{\text{NaAc}_{3.8}} = 0.0094 \times 120 = 1.128 \text{ atmospheres}$$

$$OP_{\text{HAc}_{3.8}} = 0.00495 \times 880 = 4.36 \text{ atmospheres}$$

$$\text{Total } OP_{3.8} = 5.49 \text{ atmospheres}$$

$$\text{Grams dextrose required at } p_H 3.8 = (9.00 - 1.128 - 4.36) \times 0.727 = 2.55$$

For phosphate buffer:

$$\int_{\text{KH}_2\text{PO}_4} = 0.003$$

$$\int_{\text{Na}_2\text{HPO}_4} = 0.0025$$

The use of this simple means of calculation permits preparation of solutions in which the theoretic osmotic activities agree well with experimentally determined values. The extremes of  $\Delta t$  for acetate buffer were 0.715 and 0.691; for phosphate buffer, they were 0.721 and 0.691.

In the studies on swelling, corneas and pieces of sclera were placed in 100 cc. of buffer solution and held at room temperature. Larger quantities of buffer were found unnecessary, as judged by the stability of the  $p_H$  throughout the experiments.

Swelling of the cornea is expressed as the ratio of the weight as determined at any given time to the original wet weight. In experiments with sclera, pieces weighing about 500 mg. were cut. Swelling is expressed in the same manner as that for cornea. At selected logarithmic time intervals, the weight ratios are plotted against the  $p_H$ . It is a simple matter to reconstruct the rate curves for swelling from the figures if one so desires.

The data were subjected to analysis by the chi square method.<sup>6</sup> Probabilities were read from pearsonian tables. Where chance differences in swelling existed between two values for the  $p_H$ , one of them was omitted in the plotting of data. Chance differences were found for values about the isoelectric point for the acetate buffer, and for values above  $p_H$  6.6 for the phosphate buffer. These points demonstrate the great variability of swelling in this range of  $p_H$ . Time intervals were tested for significance in the same manner.

#### RESULTS

*Cornea in Acetate Buffer.*—The weight ratio for cornea was a function of the  $p_H$ , as shown in chart 1 *A* and *B*, and increased with time to some limiting value, depending on the  $p_H$ . A definite swelling minimum was established at  $p_H$  4.6 by the sixty-third hour, which may be taken as the apparent isoelectric point of the cornea. At this point the cornea showed negative swelling in these experiments. The existence of an isoelectric point in this region was found also by Cogan and Kinsey.

The effect of failure to equilibrate the osmotic activity in the various solutions is shown in chart 1 *B*. On the alkaline side of the isoelectric point, the rate of swelling was greater in the presence of osmotic correction, although the total swelling attained at sixty-three hours was about the same. On the acid side of the isoelectric point, however, swelling was greater in both rate and amount in the absence of osmotic correction.

If the cornea was dried in air to constant weight before being placed in the buffer solutions, it swelled in the same manner as fresh cornea, as shown in chart 2. At  $p_H$  5.6 the rate of swelling after two and a half hours and the maximum of swelling at forty hours were identical with the values for the fresh cornea. However, at  $p_H$  3.6, both rate and swelling maximum were greater for dried cornea.

*Cornea in Phosphate Buffer.*—The rate of swelling of cornea in phosphate buffer was much less than that in acetate buffer (chart 3), as one would expect from the known effects of valence of acids on imbibition. In the Donnan effect, monobasic acids affect swelling of a protein according to the equation  $y(y+z)=X^2$ , while dibasic acids behave as  $y^2(y+z)=X^3$ . Great variability in swelling was found

6. Yule, G. U.: *Theory of Statistics*, ed. 10, London, Charles Griffen & Company, Ltd., 1936, p. 370.

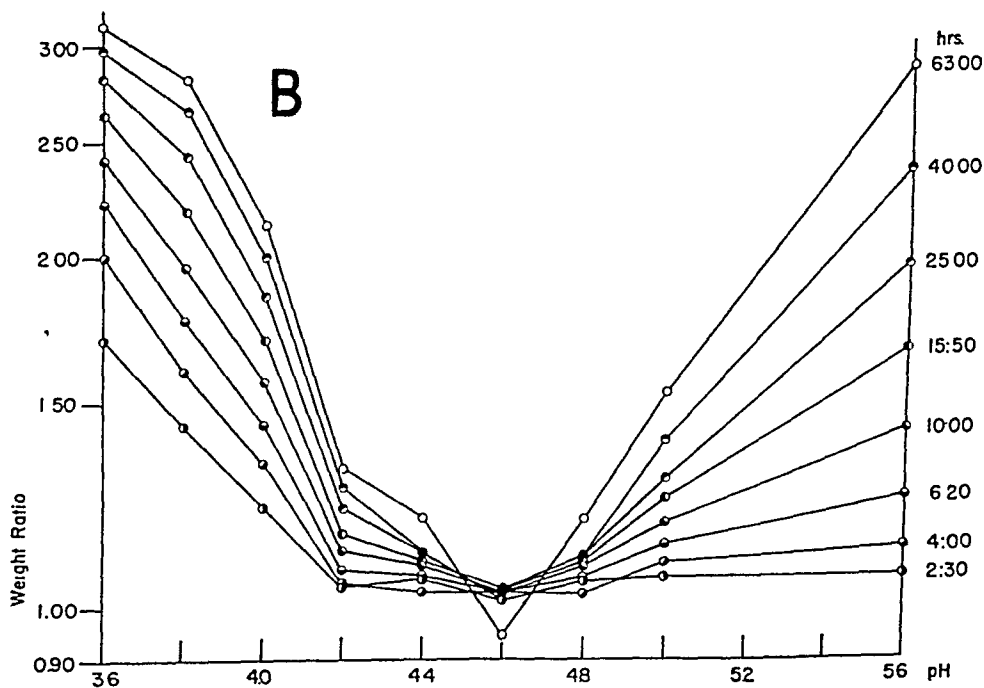
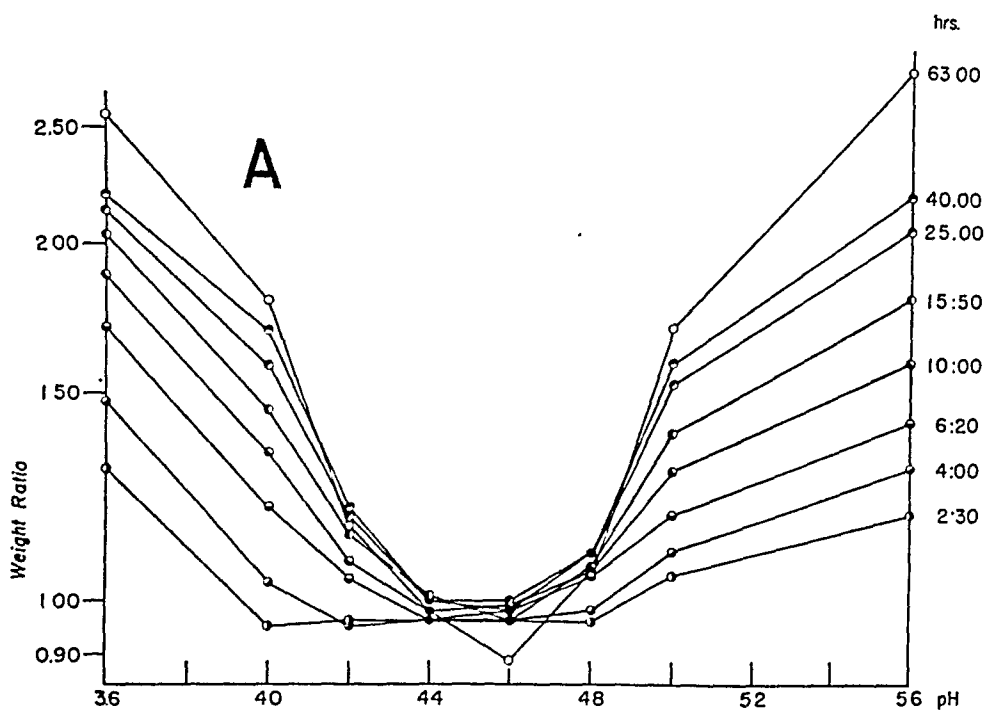


Chart 1.—*A*, swelling of cornea in isosmotic, 0.2 normal acetate buffer solutions. *B*, swelling of cornea in 0.2 normal acetate buffer solutions, without osmotic correction.

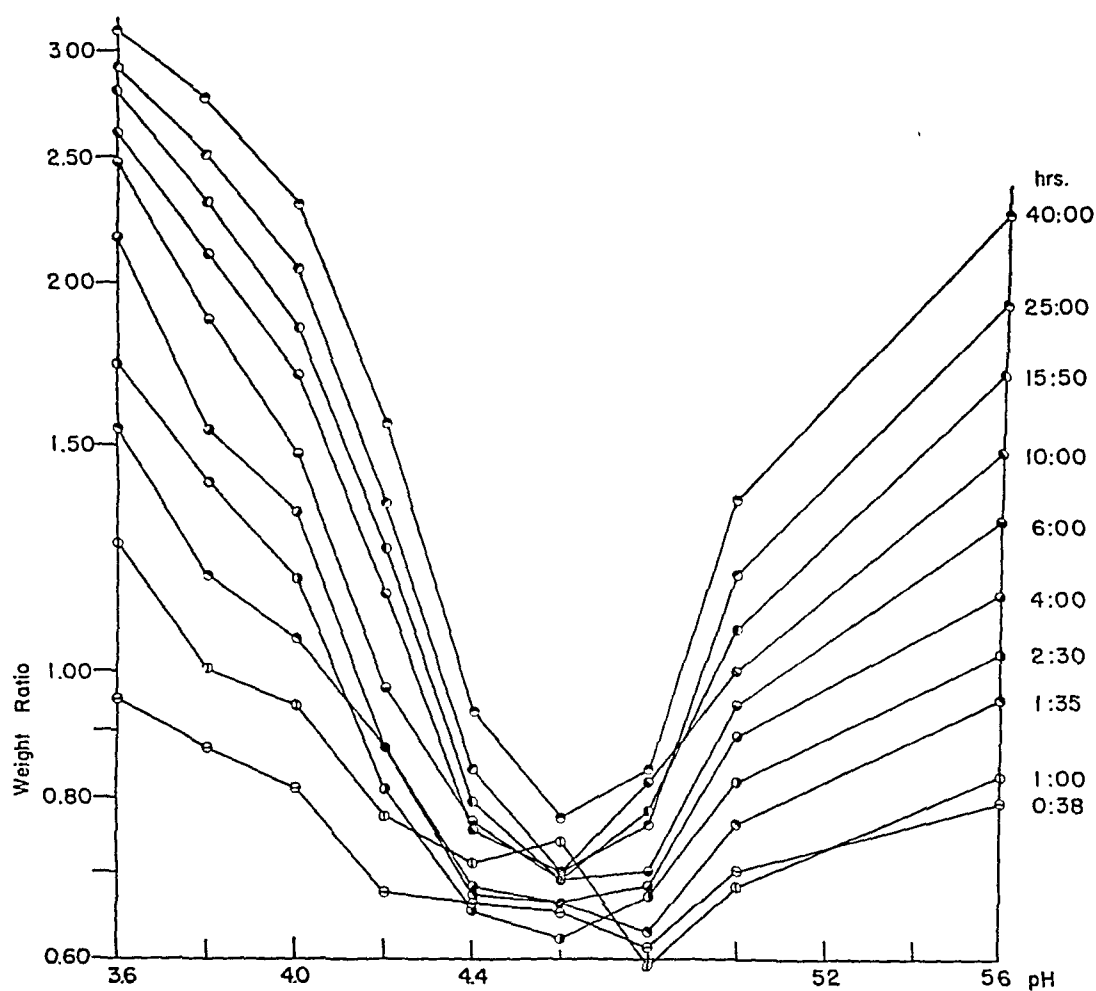


Chart 2.—Swelling of dried cornea in isosmotic, 0.2 normal acetate buffer solutions.

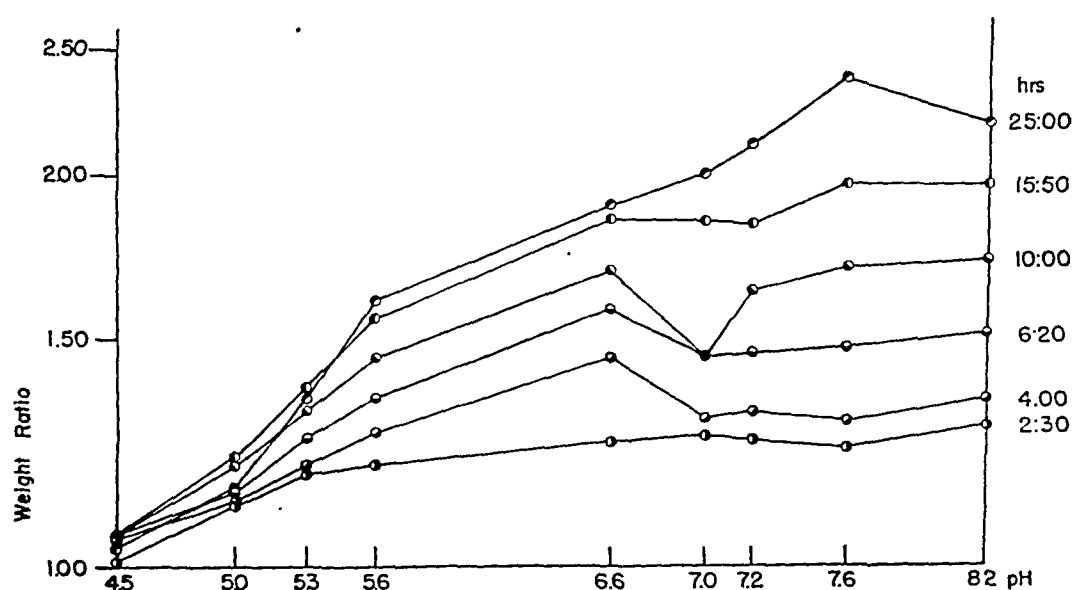


Chart 3.—Swelling of cornea in isosmotic, 0.0667 normal phosphate buffer solutions.

at a  $p_H$  above 6.6, and the points shown in the figure represent chance differences. This suggests the advisability of studying swelling in the physiologic range of  $p_H$  values with continuous recording of rate of swelling.

*Sclera in Acetate and Phosphate Buffer.*—Whereas the swelling of cornea gave the beautiful mathematical functions just presented, the striking feature of the swelling of scleral tissue under the same conditions

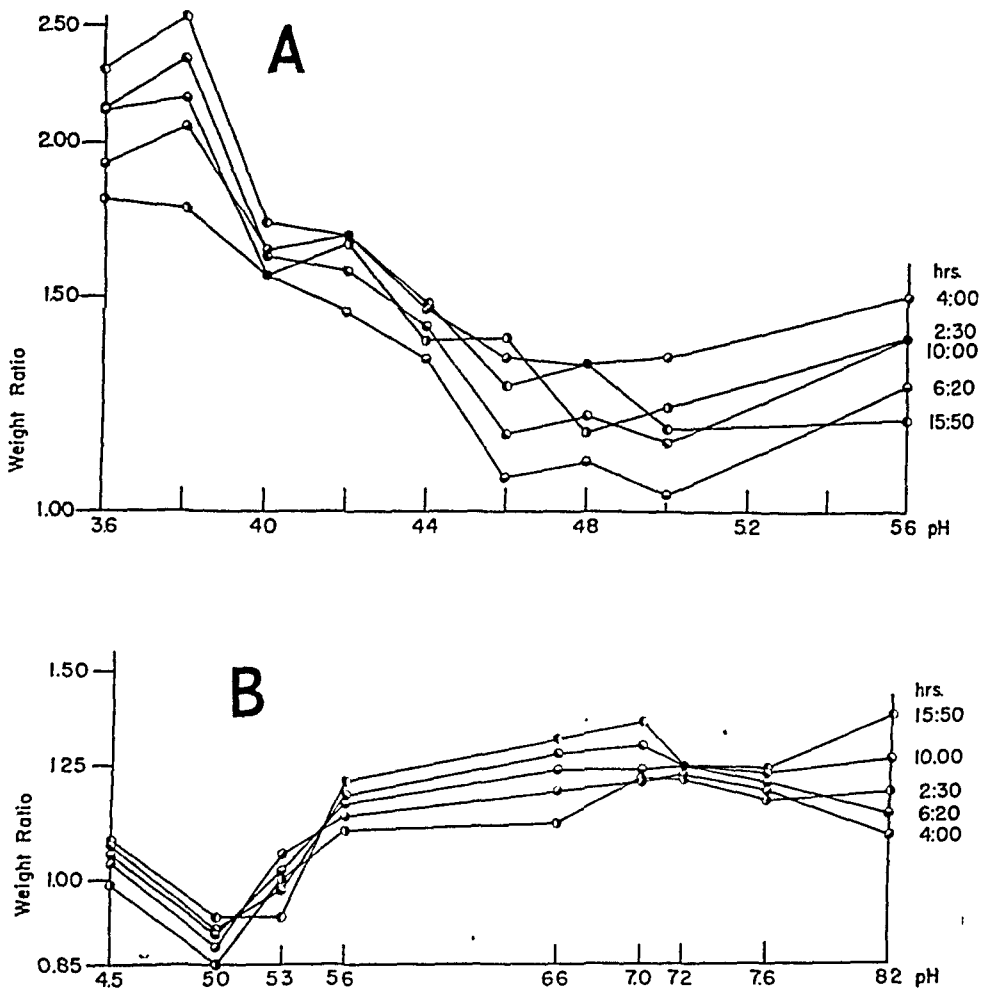


Chart 4.—*A*, swelling of sclera in isosmotic, 0.2 normal acetate buffer solutions. *B*, swelling of sclera in isosmotic, 0.0667 normal phosphate buffer solutions.

was its erratic behavior. This is well brought out by inspection of chart 4 *A* and *B*. The general configuration of chart 4 *A* suggests that scleral tissue tends to swell in a manner comparable to corneal tissue.

*Changes in Viscosity in Cornea.*—Regardless of the buffer used, corneas at  $p_H$  3.6 were in general observed to be very firm in consistency. This firmness was observed to a lesser degree in all buffers up to  $p_H$  5.0, at which point the cornea was soft. It was very soft at

$p_H$  5.6 and above. The degree of firmness or softness at the various values for the  $p_H$  was subject to some variation, according to the electrolyte added. At  $p_H$  values above the physiologic range, corneas became gelatinous and went into solution.

#### COMMENT

The cornea swells in a regular and predictable manner. The sclera, on the other hand, swells erratically. It is reasonable to postulate that, although both tissues are composed of collagenous fibers, the lamellar arrangement of fibers in the cornea permits orderly swelling of that tissue, while the dense felting of the fibers in the sclera sets up strong cohesive forces which interfere with free swelling.

Another factor is yet to be evaluated in differentiating the swelling behavior of cornea and sclera. Meyer and Chaffee<sup>7</sup> isolated a naturally occurring monosulfuric acid ester of hyaluronic acid from the cornea. The ester forms a stable complex with protein. Since this compound is not found in sclera, one may assume that it accounts for some of the differences between cornea and sclera, as well as for some of the unexpected deviations of the cornea from the behavior of gels in general—for example, the failure of imbibition to correlate with viscosity. This compound remains to be isolated and studied, in order that its role in the swelling behavior of the cornea may be assessed.

Heringa and associates<sup>8</sup> studied the effect of extracting the mucoid on swelling of the cornea in 100 per cent water vapor. Swelling was thereby reduced from thirty to thirteen times the dry weight. Water absorption isotherms for cornea and sclera were found to coincide below an 80 per cent saturation of the atmosphere but diverged widely above this point.

Gelatin gels have been so thoroughly studied that it may be profitable to point out the similarities and differences in behavior of gelatin and the substantia propria (collagenous fibers) of the cornea.

When gelatin swells in saline solutions, the concentration of salt in the swollen particles is practically the same as that in the surrounding medium, as though water went in by capillarity. Holt and associates<sup>9</sup>

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7. Meyer, K., and Chaffee, E.: Mucopolysaccharide Acid of Cornea and Possible Relation to the "Spreading Factor," *Proc. Soc. Exper. Biol. & Med.* **43**:487-489, 1940; The Mucopolysaccharide Acid of the Cornea and Its Enzymatic Hydrolysis, *Am. J. Ophth.* **23**:1320-1325, 1940.

8. Heringa, G. C., and Weidinger, A.: Structure and Importance of Connective Tissue: XI. Water Binding in the Intermediary Substance, *Nederl. tijdschr. v. geneesk.* **84**:4907-4917, 1940. Leyns, W. F.; Heringa, C., and Weidinger, A.: Water Binding Capacity of Cornea, *Acta brev. Neerland.* **10**:25-26, 1940.

9. Holt, M., and Cogan, D. G.: The Cornea: VIII. Permeability of the Excised Cornea to Ions, as Determined by Measurements of Impedance, *Arch. Ophth.* **35**:292-298 (March) 1946.



showed that the resistance of corneal stroma to the passage of ions is about that offered by an equivalent volume of isotonic solution of sodium chloride. As for nonpolar substances, Collander<sup>10</sup> found that gelatin membranes show no preferential permeability to lipid substances. Swan and White<sup>11</sup> showed that the corneal stroma permits ready entrance of polar and surface-inactive compounds, while nonpolar and surface-active compounds pass less readily. On the other hand, the presence of the corneal epithelium causes nonpolar compounds to penetrate the stroma more readily and polar compounds less readily. Cogan and co-workers<sup>12</sup> confirmed these findings, emphasizing that purely water-soluble substances do not pass the epithelium and purely fat-soluble substances do not pass the stroma, and pointed out that substances which pass whole cornea have biphasic solubilities, with the exception of water.

The isoelectric point of the substantia propria of the cornea corresponds well with that for pure gelatin. The fact that the cornea may be dried to constant weight and then found to follow a swelling curve similar to that for normal cornea shows the minimum of "hysteresis" effect. The latter term is used to denote the "memory" of colloid systems and indicates the effect of previous history on behavior. This finding is an important practical point in the problem of corneal transplantation and represents an interesting departure from pure gelatin, since Gortner and Hoffman<sup>13</sup> found that drying had a profound effect on rate of rehydration and maximum imbibition of gelatin particles.

It is interesting to note that mechanical distortion of a gelatin block produces an optical birefringence similar to that seen in cornea. In gelatin, however, the anisotropy disappears slowly on release of pressure, while in the cornea the return to the original state is sudden, no doubt due to elastic components of the substantia propria. This phenomenon probably represents in both instances a rod-structural type of birefringence. Further comment on its causation and its significance in the transparency of the cornea will be made in the second paper.

No one mechanism has been found adequate to explain the swelling of proteins under all conditions. Using the roentgen ray diffraction

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10. Collander, R.: Einige Permeabilitätsversuche mit Gelatinemembranen, *Protoplasma* **3**:213-222, 1928.

11. Swan, K. C., and White, N. G.: Corneal Permeability: I. Factors Affecting Penetration of Drugs into the Cornea, *Am. J. Ophth.* **25**:1043-1057, 1942.

12. Cogan, D. G.; Hirsch, E. O., and Kinsey, V. E.: The Cornea: VI. Permeability Characteristics of the Excised Cornea, *Arch. Ophth.* **31**:408-412 (May) 1944. Cogan, D. G., and Hirsch, E. O.: The Cornea: VII. Permeability to Weak Electrolytes, *ibid.* **32**:276-282 (Oct.) 1944.

13. Gortner, R. A., and Hoffman, W. F.: The Imbibition of Gelatin Dried as a Gel and as a Sol, *J. Phys. Chem.* **31**:464-466, 1927.

technic, Katz <sup>14</sup> distinguished intermicellar, intramicellar and permutoid (chemical compound formation) types of swelling. Histologic sections of the cornea stained with Mallory's aniline blue show that the swelling is both between and within the lamellas.

In summary, it may be said that the fibrous tunic of the eye is analogous to gelatin in swelling behavior. The significance of this observation is that the cornea and sclera are both lyophilic colloid systems and are subject to the same general rules of behavior as are such systems in general. Such differences as are noted in swelling behavior between cornea and sclera can be explained as largely due to differences in mechanical arrangement of the fibers. The presence of hyaluronosulfuric acid in cornea and its absence from sclera is another factor yet to be evaluated.

Dr. R. H. Peckham made mathematical examination of the data and constructed the figures.

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14. Katz, J. R.: The Laws of Swelling, *Tr. Faraday Soc.* **29**:279-297, 1933

## THE CORNEA

### II. Factors Affecting the Transmission of Visible Light by the Fibrous Tunic of the Eye

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THE CLINICAL problem posed by opacification of the cornea stimulated an early interest in the factors responsible for transparency of this tissue and the possible explanations for its striking dissimilarity to the sclera. The most recent attack on this problem has been made by Cogan and Kinsey,<sup>1</sup> who reviewed the pertinent work before their time. These authors emphasized the water content of the cornea as the chief determining factor in the transparency of this tissue and as responsible for the optical difference between cornea and sclera. According to their concept, the cornea is endowed with a dehydrating mechanism (in the form of semipermeable endothelium and epithelium) to keep down its water content. When this mechanism fails, swelling, and therefore opacification, occurs. The sclera, on the other hand, is said to be opaque because of the absence of any such mechanism.

While studying swelling of the cornea, we had ample opportunity to determine the effect of water content and other factors on the optical properties of the cornea. In the present paper we shall show that there is a rough inverse relation between the degree of swelling and the degree of turbidity of the cornea under the conditions of our experiments and, further, that the cornea may remain transparent despite any degree of swelling. The factors responsible for corneal transparency are analyzed, and the theoretic approach to the clinical problem of corneal opacity is given.

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This study was supported in part by a grant from the John and Mary R. Markle Foundation.

From the Departments of Ophthalmology and Biochemistry, Temple University School of Medicine.

1. Cogan, D. G., and Kinsey, V. E.: The Cornea: V. Physiologic Aspects, *Arch. Ophth.* 28:661-669, (Oct.) 1942; *Physiologic Studies on the Cornea*, *Science* 95:607-608, 1942.

## METHODS AND MATERIALS

The technics for studying beef corneas reported in the previous paper<sup>2</sup> were used. All buffer solutions were adjusted to the same osmotic activity (9.00 atmospheres) as before. An arbitrary scale was used for evaluating the degree of turbidity of the cornea. A black line on a piece of white paper was viewed through the cornea. Recordings of turbidity were made as 0, 1, 2, 3 and 4, in which 0 indicated normal cornea, 4 a completely opaque cornea and 1, 2 and 3 inter

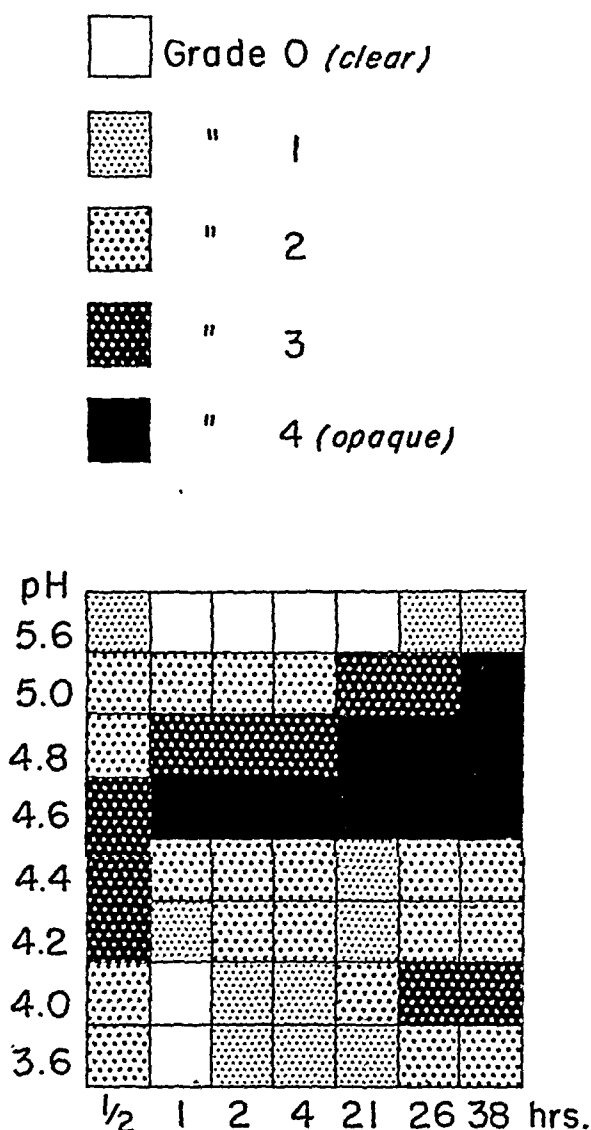


Chart 1.—Changes in turbidity in corneas in isosmotic, 0.2 normal acetate buffer solutions.

mediate stages. Control observations by independent observers quickly established the reliability of these readings. After practice was gained, plus values were used as interpolations in these readings. Obviously, photographic transmission data would represent more accurate nephelometry, but for present purposes the arbitrary scale is in many ways superior.

2. Hart, W. M., and Chandler, B. F.: The Cornea: I. Swelling Properties of the Fibrous Tunic of the Eye, Arch. Ophth. 40:601 (Dec.) 1948.

In constructing charts 1, 2, 3 and 4, the five arbitrary steps of optical difference were represented by areas of stippling and solid black. All turbidity readings were reported after removal of the epithelium. In determining the effects of electrolytes on turbidity, each solution was made 0.01 normal with respect to the electrolyte in question.

### RESULTS

*Degree of Swelling.*—The weight ratio for cornea is a function of the  $p_H$ , as shown in figure 1 *A* and *B* of the first paper, and increases with time to some limiting value, depending on the  $p_H$ .<sup>3</sup> If turbidity

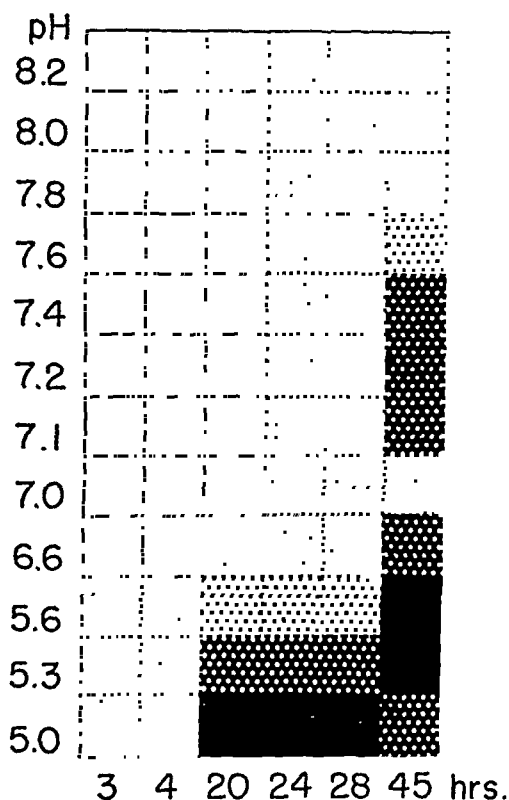


Chart 2.—Changes in turbidity in corneas in isosmotic, 0.0667 normal phosphate buffer solutions.

is plotted with coordinates of weight ratio and  $p_H$ , weight ratio and time, and  $p_H$  and time, one finds that turbidity is independent of time and the weight ratio. Although weight ratio and turbidity are both functions of the  $p_H$ , they relate to the  $p_H$  in an inverse manner, as shown in chart 5. In addition to the influence of the  $p_H$ , turbidity is affected by the presence of certain electrolytes, as noted later. In acetate buffer, the turbidity is grade 4 at the isoelectric point ( $p_H$  4.6), where the cornea actually loses in weight, while at  $p_H$  5.6 and  $p_H$  3.6, where swelling is great, the transmission of light is excellent.

3. The extent of swelling to be expected at each  $p_H$  value for any particular buffer may be found by consulting our previous paper.

If the cornea is placed in 0.001 normal hydrochloric acid, as shown in table 1, the swelling ratio is 2.0 at forty-eight hours, and grade 4 turbidity is reached by the twentieth hour. When the cornea is placed in 0.01 normal hydrochloric acid, the weight ratio is 4.5 at forty-eight hours, while the turbidity remains at grade 0 throughout the period.

TABLE 1.—*Swelling and Turbidity of Corneas in Isosmotic Solutions of Hydrochloric Acid at  $p_H$  2 and  $p_H$  3*

Time, Hr.	$p_H$ 2 0.01 Normal Hydrochloric Acid Solution		$p_H$ 3 0.001 Normal Hydrochloric Acid	
	Weight, Mg.	Turbidity	Weight, Mg.	Turbidity
0.....	370	0	405	0
1.....	...	0	690	0
2.....	950	0	810	0+
3.....	1,160	0+	875	1
5.....	1,300	0+	955	3
7.....	...	..	950	3+
19.....	1,590	0+	910	4
22.....	1,615	0+	915	4
24.....	1,640	0	960	4
27.....	1,655	0	905	4
30.....	1,650	0	870	4
44.....	1,700	0	800	4
48.....	1,680	0	850	4

*Effect of Previous Drying.*—Cornea which has first been dried in air shows improved transmission of light in acetate buffer and is at least as good as fresh cornea in phosphate buffer. In chart 3, for example, the turbidity is only grade 1 after seven hours at the isoelec-

TABLE 2.—*Changes in Turbidity in Air-Dried and Ether-Extracted Corneas in Acetate Buffer Solutions*

Time, Hr.	$p_H$						
	3.6	4.0	4.4	4.6	4.8	5.0	5.6
0.....	0	0	0	0	0	0	0
¼*.....	1	1	1	1	0+	0+	1
2.....	1	0	0	0	0	0	0+
4.....	2+	1+	1+	1	1	2	1+
20.....	2	3	3	2	1	3	2
25.....	3	3+	3	2	1+	3	2+
49.....	3+	3+	3	3	..	4	3

\* The reading at the end of one-fourth hour was taken in the presence of epithelium.

tric point, while it is grade 4 for fresh cornea. The findings for phosphate buffer are shown in chart 4. The improved transmission of light of previously dried cornea, which is especially evident at the isoelectric point, suggests the operation of some factor, as yet unknown, other than the  $p_H$ .

In order to determine whether the improvement in turbidity was related to the fat content of the cornea, dried corneas were subjected to continuous extraction with ether for twenty-four hours before the swelling experiments were begun. As shown in table 2, the result is not significantly different from that for dried, nonextracted cornea.

*Temperature.*—When the temperature was lowered to 10 C., as shown in table 3, no noticeable change was produced except for a tendency of the maximum turbidity to shift from a  $p_H$  of 4.6 to a  $p_H$  4.8. Increase in the temperature to 40 C. produced obvious improvement in

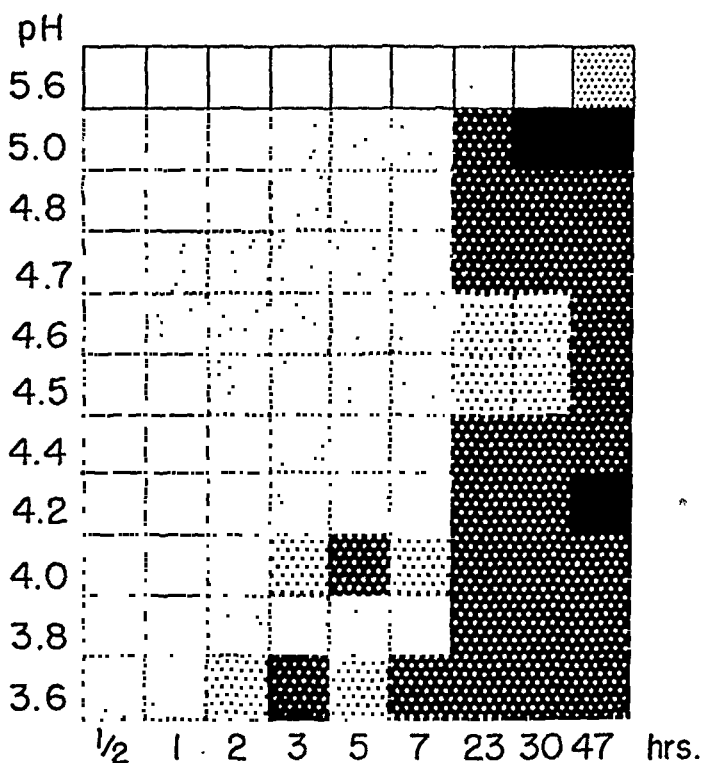


Chart 3.—Changes in turbidity of air-dried corneas in isosmotic, 0.2 normal acetate buffer solutions.

optical effect, especially about the isoelectric point, as shown in table 4. The degree of swelling at these temperatures was of the same order as that at 25 C. (including negative swelling at the isoelectric point).

*Electrolytes.*—The left column of table 5 shows turbidity readings on the cornea in acetate buffer at  $p_H$  4.6 with no additional salts. Some ions, e. g.,  $Na^+$ ,  $Fe^{++}$ ,  $Ca^{++}$ ,  $SCN^-$  and  $PO_4^{---}$ —lessen turbidity at this  $p_H$ . At  $p_H$  3.6, all added ions produced some increase in turbidity, as seen in table 6. Table 7 shows considerable variation at  $p_H$  5.6. The  $PO_4^{---}$  ion caused no change in turbidity.  $Cu^+$  and  $Ba^{++}$ , in particular, caused a notable increase in turbidity. All other ions increased turbidity to some extent.

. *Opacity of the Cornea.*—Opacities of the cornea are common in cattle. Eyes were brought to the laboratory with dense white opacities; many had deep ulcer craters and profuse fibroblastic invasion. Clearing of such corneas may be produced in one of two ways: (1) by simply

TABLE 3.—*Changes in Turbidity of Corneas in Acetate Buffer with Added Dextrose, at 10 C.*

Time, Hr.	$p_H$							
	3.6	4.0	4.2	4.4	4.6	4.8	5.0	5.6
0.....	0	0	0	0	0	0	0	0
$\frac{1}{2}$ *.....	2+	1+	1	1	1	0+	0	0
$\frac{3}{4}$ .....	2	4	3+	3	1+	2	0+	0
1.....	0	2+	3+	2+	2	2	0	0
2.....	1	1+	4	2+	3	4	1+	0+
3.....	0+	1	2+	3+	3	3+	1+	0
4.....	1	1+	2	3+	3	4	1+	0
8.....	1+	2	2+	4	4	4	2	0
22.....	1+	2	3	4	3	4	2+	0
26.....	1+	2	3	3+	3+	4	2+	0
50.....	1+	2	3	4	3+	4	3	0
75.....	2	3	3	4	3+	4	3	0
100.....	2	3	3	4	3	4	3	1+

\* The first reading, at one-half hour, was taken in the presence of epithelium.

TABLE 4.—*Changes in Turbidity of Corneas in Acetate Buffer with Added Dextrose, at 40 C.*

Time, Hr.	$p_H$							
	3.6	4.0	4.2	4.4	4.6	4.8	5.0	5.6
0.....	0	0	0	0	0	0	0	0
$\frac{1}{2}$ .....	1	1	1+	1+	1+	1+	0	0
$\frac{3}{4}$ .....	1	1	1+	1+	1+	1+	0+	0
1.....	1	1	1+	1+	1+	1+	0+	0+
2.....	1+	1+	2	1+	1+	2	1+	0+
3.....	1+	1+	1+	1+	1+	1+	1+	1
4.....	1+	1+	1+	1+	1+	1+	1+	1
8.....	2+	3+	2+	2	2	1+	1	0+
22.....	2+	2+	2+	2	2	2	1+	1+
26.....	3	3	3	1+	1+	1+	2	0+
50.....	3+	3+	2+	1+	1+	2	2+	1+
75.....	4	4	3	1+	1+	1+	2	2
100.....	4	4	3	1+	1+	1+	1+	2

drying in air, or (2) by swelling in 0.01 normal hydrochloric acid, phosphate or acetate buffer at proper hydrogen ion concentration. When the dried corneas are rehydrated in these solutions they follow normal swelling curves and remain clear.

#### COMMENT AND CONCLUSIONS

Throughout these observations a rough inverse relation with respect to the  $p_H$  existed between the degree of swelling and the turbidity of the



cornea. In addition to the influence of the  $p_H$ , turbidity was specifically affected by certain ions, as already noted.

M. Fischer<sup>4</sup> concluded that simple absorption of water does not lead to corneal opacity. He studied the effects of ions on swelling and

TABLE 5.—*Effects of Ions on Turbidity of Corneas in Acetate Buffer Solution at  $p_H$  4.6*

Time, Hr.	Buffer Alone	Ca <sup>++</sup>	K <sup>+</sup>	Ba <sup>++</sup>	Cu <sup>+</sup>	Li <sup>+</sup>	Mg <sup>++</sup>	Fe <sup>++</sup>	Na <sup>+</sup>	SCN <sup>-</sup>	Citrate	SO <sub>4</sub> <sup>-</sup>	PO <sub>4</sub> <sup>---</sup>
¼.....	3*	2	2	2+	3	2	2	2	2+	..	2+	..	..
½.....	4	..	..	..	..	..	..	..	..	3	2+	2+	2
1.....	4	2+*	3+*	3+	3+*	3+*	3+*	3+*	3*	3*	3+*	3*	3
2.....	4	3	4	4	4	4	3+	3+	3	3	3+	4	3+
3.....	4	3	4	4	4	4	3+	3+	3	3+	4	3+	3+
4.....	4	3+	4	4	4	4	4	3+	3	3+	4	3+	3+
20.....	4	3	4	4	4	4	4	3+	3	3+	4	4	4

\* Epithellum removed; epithellum remained on in the solution containing barium.

TABLE 6.—*Effects of Ions on Turbidity of Corneas in Acetate Buffer Solution at  $p_H$  3.6*

Time, Hr.	Buffer Alone	Ca <sup>++</sup>	K <sup>+</sup>	Ba <sup>++</sup>	Cu <sup>+</sup>	Li <sup>+</sup>	Mg <sup>++</sup>	Fe <sup>++</sup>	Na <sup>+</sup>	SCN <sup>-</sup>	Citrate	SO <sub>4</sub> <sup>-</sup>	PO <sub>4</sub> <sup>---</sup>
¼.....	..	3+	3	3+	3+	3	4*	3+*	3+*	..	..	..	..
½.....	2+	..	..	..	..	..	2	..	..	2+*	2+*	2+*	4*
1.....	0+*	1*	0+*	1*	1+*	1+*	2+	1	1+	2	1+	2	1+
2.....	1+	2	1	1+	2	1	2	1+	2	1+	2	2	2
3.....	1+	2	1+	2	2	2	2	2	2	2	1+	2	2
4.....	..	1+	2	2	2+	2+	2+	1+	2	2	2	2	2
20.....	1	2+	2+	3	2+	2	2	2	2	2	2	3	2+

\* Epithellum removed.

TABLE 7.—*Effects of Ions on Turbidity of Corneas in Acetate Buffer Solution at  $p_H$  5.6*

Time, Hr.	Buffer Alone	Ca <sup>++</sup>	K <sup>+</sup>	Ba <sup>++</sup>	Cu <sup>+</sup>	Li <sup>+</sup>	Mg <sup>++</sup>	Fe <sup>++</sup>	Na <sup>+</sup>	SCN <sup>-</sup>	Citrate	SO <sub>4</sub> <sup>-</sup>	PO <sub>4</sub> <sup>---</sup>
¼.....	..	0	0—	0—	0—	0—	0	1	0	..	..	..	..
½.....	1	..	..	..	..	..	..	2—	..	0—	1	0—	0
1.....	0—*	1	1—	2—	3—	2	2	3	2	2	1	2	0—
2.....	0—	2—	1*	3	3—	3	2	2—	2	2	2	2	0—
3.....	0—	2—	1	3	4	2—	2	2—	2	1—	2	2	0—
4.....	0—	2	1	3—	4	3	2	2	2	2	2	2	0—
20.....	0—	1*	1—	2*	4	2*	1*	2	3	2—	1*	2—	1—
46.....	1	1	0—	2	4	1	1	2	3	2—	1	0—*	1—

\* Epithellum removed; epithellum remained in solutions containing Cu<sup>+</sup>, Fe<sup>++</sup>, Na<sup>+</sup>, PO<sub>4</sub><sup>---</sup> and SCN<sup>-</sup>.

the transmission of light by the cornea in 1/110 normal solutions of hydrochloric acid. Besides noting a discrepancy in the amount of water imbibed and the degree of turbidity of the cornea, he found that

4. Fischer, M.: Oedema, New York, John Wiley and Sons, Inc., 1910, p. 136.

citrate, acetate and sulfate ions inhibited corneal opacity in the acid solutions, while thiocyanate, nitrate, bromide and chloride ions favored corneal opacity. Fischer found also that subconjunctival injection of 5 to 15 drops of "hypotonic" or "hypertonic" solutions of sodium citrate (one-eighth to one-sixth molar) lowered the tension in glaucomatous eyes and caused improvement in the steamy cornea. Although we have not attempted such clinical observations, we have not found that citrate influences cornea favorably in the presence of the acetate ion.

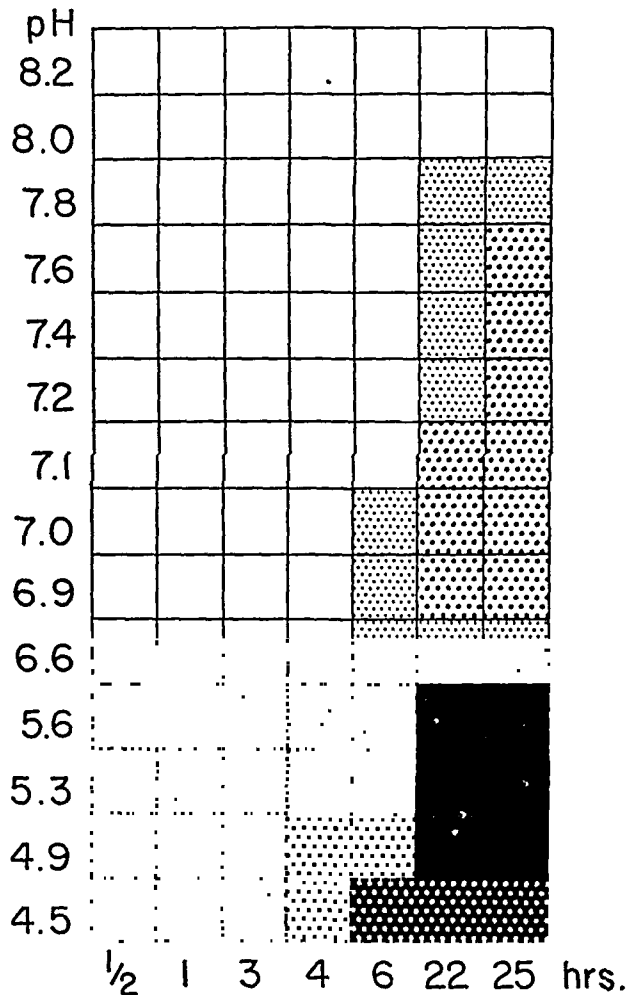


Chart 4.—Changes in turbidity of air-dried corneas in isosmotic 0.0667 normal phosphate buffer solutions.

F. P. Fischer<sup>5</sup> found that reducing the water content of the sclera below 40 per cent or increasing it above 80 per cent rendered this tissue transparent. Although we have not attempted to verify these limits, we have found Fischer's observation correct provided one controls the hydrogen ion concentration and ionic composition of the medium in which the sclera swells.

5. Fischer, F. P.: Experimentelle Untersuchungen an der Lederhant, Arch. f. Augenh. 97:467, 1926, cited by Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1946, vol. 1, p. 477.

It is well known that swelling of the cornea resulting from damage to its membranes (as in glaucoma) causes clouding. We believe that this effect is determined by the "state" of the water which enters the cornea. Biomicroscopy and fixed histologic sections show that in such conditions water enters the cornea as fine droplets, which remain discrete and progress through the thickness of the substantia propria. This effect, too well known to be described here, is spoken of as a "bedewing" or "steaminess," terms which are descriptively accurate in view of the dispersion of light which results. The semipermeable features of the endothelium and epithelium (with respect to sodium chloride), so well demonstrated by Cogan and Kinsey, may thus subserve the interests of corneal transparency by keeping down the water content of the substantia propria and thereby preventing this effect, although an increase in water content per se does not produce opacification. The possible effects of changes in hydrogen ion concentration

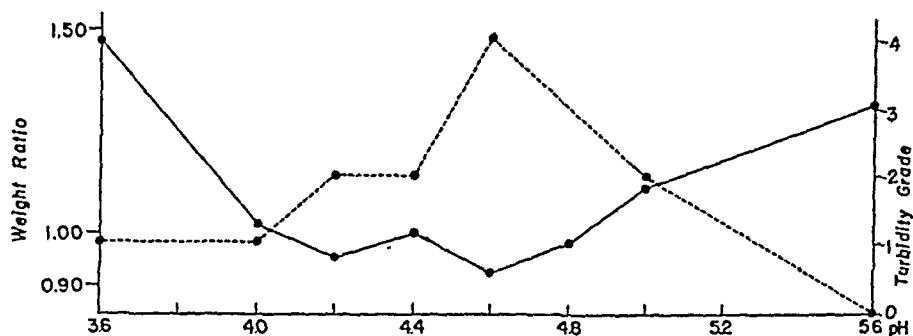


Chart 5.—Curves for weight ratio and turbidity of cornea in 0.2 normal acetate buffer solution at end of four hours, showing a roughly inverse relation between swelling and turbidity as related to the  $pH$ .

and alterations in electrolyte content in such circumstances are thus far unknown but may be presumed to play a part.

In view of the inverse relation between swelling and turbidity of the cornea, the effects of electrolytes, temperature, hydrogen ion concentration and other factors, and the fact that the sclera becomes transparent when properly hydrated, it is obvious that one must look for explanations other than the degree of turgescence or deturgescence to account for the optical difference between cornea and sclera. In so doing, one may list at least three possibilities: (1) differences in refractive index between solvent water and micelles; (2) birefringence phenomena resulting from the fibrillar structure of the fibrous tunic, and (3) the state or dispersion of water in the cornea and sclera, as previously noted.

It is obvious that if the refractive index of the solvent water in the cornea becomes very different from that of the particles, turbidity results. The first step, then, is to list the factors which may affect the refractive index of each. Affecting the micellar refractive index are

(1) temperature, (2) electrolytes, (3) isoelectric point, (4) hydrogen ion concentration, (5) dissociation, (6) mechanical stresses (as in birefringence), (7) hysteresis and (8) coacervate formation (due to protein-lipid-carbohydrate complexes).

Affecting the refractive index of the solvent water are (1) temperature, (2) electrolytes, (3) hydrogen ion concentration, (4) nonelectrolytes and (5) surface tension. The operation of most of these factors is readily apparent in the data presented in this paper and requires no further comment. No doubt there are others which we have not listed.

In consideration of the birefringence phenomenon, we have the well known observation that pressure on the intact eye produces clouding of the cornea. When this pressure is released, the cornea suddenly returns to its original clear state. Cogan and Kinsey<sup>1</sup> accepted the theory of Verrijp that pressure on the eye forces fluid from the structural components into the interstices. The difference in the refractive indexes of the two fluids, according to this theory, becomes apparent as a clouding. It should be pointed out, however, that such pressure is distributed equally in all directions and therefore should tend to force as much fluid in as is forced out of the structural components. We believe this phenomenon may be a true birefringence with the optical axis perpendicular to the corneal curvature at all points. When pressure is applied to the eye, this axis is rotated into the plane of the cornea, and interference with transmission of light results. Such a hypothesis has the merit at least of being amenable to experimental test and will be the subject of our further investigation.

In proposing a theory to account for all the phenomena observed thus far, the cornea may be said to be transparent for two reasons: (1) The spatial arrangement of its fibers has permitted a balance of intramucellar and extramucellar fluid, such as would keep the refractive indexes in the two situations equivalent, and/or (2) the spatial arrangement and organizational plan of fibers have permitted the orderly birefringent mechanism already referred to. It will be recalled that passage of a needle into the living cornea produces a persistent opacity at the site. This opacity is probably due to mechanical disarrangement of the fibers, which produces a local effect similar to that seen when the whole eye is pressed. The distortion of fiber pattern produced by fibroblastic retraction produces a similar effect in a healed corneal lesion. The use of ethyl morphine hydrochloride U. S. P. in treatment of corneal opacity, although of doubtful efficiency, has a good foundation in that its irritating properties cause it to act as a lymphagogue, with a tendency to mechanical redispersion of the corneal fibers.

Drying causes corneal opacities to disappear. When such corneas are rehydrated, the opacities do not reappear. Here, again, the effect

It is well known that swelling of the cornea resulting from damage to its membranes (as in glaucoma) causes clouding. We believe that this effect is determined by the "state" of the water which enters the cornea. Biomicroscopy and fixed histologic sections show that in such conditions water enters the cornea as fine droplets, which remain discrete and progress through the thickness of the substantia propria. This effect, too well known to be described here, is spoken of as a "bedewing" or "steaminess," terms which are descriptively accurate in view of the dispersion of light which results. The semipermeable features of the endothelium and epithelium (with respect to sodium chloride), so well demonstrated by Cogan and Kinsey, may thus subserve the interests of corneal transparency by keeping down the water content of the substantia propria and thereby preventing this effect, although an increase in water content per se does not produce opacification. The possible effects of changes in hydrogen ion concentration

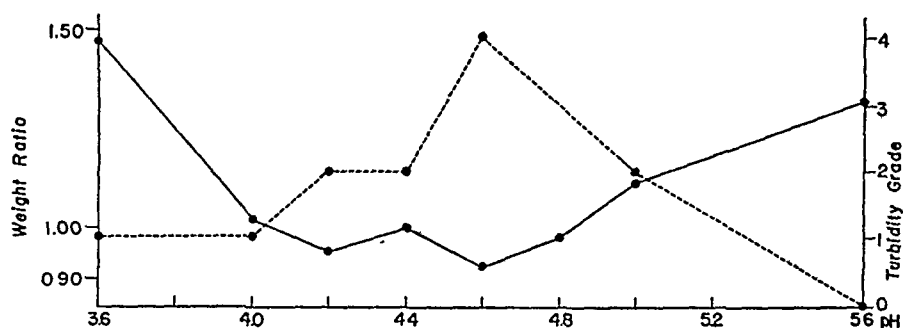


Chart 5.—Curves for weight ratio and turbidity of cornea in 0.2 normal acetate buffer solution at end of four hours, showing a roughly inverse relation between swelling and turbidity as related to the  $p_H$ .

and alterations in electrolyte content in such circumstances are thus far unknown but may be presumed to play a part.

In view of the inverse relation between swelling and turbidity of the cornea, the effects of electrolytes, temperature, hydrogen ion concentration and other factors, and the fact that the sclera becomes transparent when properly hydrated, it is obvious that one must look for explanations other than the degree of turgescence or deturgescence to account for the optical difference between cornea and sclera. In so doing, one may list at least three possibilities: (1) differences in refractive index between solvent water and micelles; (2) birefringence phenomena resulting from the fibrillar structure of the fibrous tunic, and (3) the state or dispersion of water in the cornea and sclera, as previously noted.

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In consideration of the birefringence phenomenon, we have the well known observation that pressure on the intact eye produces clouding of the cornea. When this pressure is released, the cornea suddenly returns to its original clear state. Cogan and Kinsey<sup>1</sup> accepted the theory of Verrijp that pressure on the eye forces fluid from the structural components into the interstices. The difference in the refractive indexes of the two fluids, according to this theory, becomes apparent as a clouding. It should be pointed out, however, that such pressure is distributed equally in all directions and therefore should tend to force as much fluid in as is forced out of the structural components. We believe this phenomenon may be a true birefringence with the optical axis perpendicular to the corneal curvature at all points. When pressure is applied to the eye, this axis is rotated into the plane of the cornea, and interference with transmission of light results. Such a hypothesis has the merit at least of being amenable to experimental test and will be the subject of our further investigation.

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Drying causes corneal opacities to disappear. When such corneas are rehydrated, the opacities do not reappear. Here, again, the effect

would seem to be one of rearrangement of the corneal fibers. The translucency of sclera on dehydration has the same significance as the clearing of corneal opacity on drying.

The sclera apparently becomes opaque in embryonic development as a result of its closely felted structure, which (1) does not permit dispersion of its fibers and free interchange of fluid constituents and (2) distorts the optic axis of the system of birefringence. Contrary to the conclusions of Cogan and Kinsey,<sup>1</sup> the difference in optical behavior between the cornea and the sclera has a "histologic counterpart," as is evident from the known differences in arrangement of the fibers in the two tissues, which, in turn, are reflected in the differences in swelling behavior.<sup>2</sup>

It is of importance to know that corneal opacities are reversible processes. Although it is a long way from these in vitro observations to therapeutic application, the first step has been made when the prevalent notion that ingrowth of fibroblasts dooms the cornea to permanent and irreversible opacity has been dispelled.

The scant hysteresis in corneal swelling suggests transplantation from stored material. It would be necessary, of course, to control carefully the rehydration of the dried tissue in order to insure transparent implants.

Studies on scattering of light in gelatin have no specific application to the ocular problem, but serve to demonstrate that one is dealing with similar phenomena in the matter of light transmission. The main variables affecting the light-scattering intensity in gelatin are temperature, the hydrogen ion concentration of the solution and the concentration of gelatin. Dhéré and Gorgolewski<sup>6</sup> found that purified gelatin solutions are strikingly turbid at temperatures below 30 C. Addition of acids or bases strongly diminished turbidity, as did warming to a temperature of over 30 C. These authors also found that scattering of light in gelatin is greatest at the isoelectric point. The cornea likewise shows greatest scattering of light at the isoelectric point, as well as the qualitative effects of change in acidity and variation in temperature, similar to those found for gelatin. The behavior of the cornea, however, is only analogous to gelatin, and differences are to be expected, since different specimens of gelatin will show specific characteristics. Lowering of temperature to 10 C. produces no noticeable change in the cornea except for a tendency for the maximum turbidity to shift from a  $p_H$  of 4.6 to one of 4.8. Increase in the temperature to above 40 C. produces marked optical improvement in the cornea, especially about the iso-

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6. Dhéré, C., and Gorgolewski, M.: *Recherches sur les propriétés chimiques de la gélatine déminéralisée*, J. de physiol. et de path. gén. **12**:645-656, 1910.

electric point. Dexter and Kraemer<sup>7</sup> reported that a change of a fraction of a  $p_H$  unit at the isoelectric point caused scattering of light in their specimen of gelatin to change as much as "1,000 per cent," a value which we presume to mean a tenfold change. We have not noted any such effect in the cornea.

Gerngross<sup>8</sup> found that neutral salts and nonelectrolytes, such as alcohol, urea and amino acids, diminish turbidity in gelatin, but to a less extent than do changes in acidity. Fischer<sup>4</sup> found that nonelectrolytes inhibit corneal opacity. We have found differences in the effects of the presence of certain electrolytes under the conditions of our experiments, as noted in the experimental results.

Sheppard and McNally<sup>9</sup> observed that when gelatin is stretched or otherwise deformed while being dried, subsequent swelling occurs anisotropically, the most rapid swelling being at right angles to the direction of deformity.

In summary, we find that the transmission and diffusion of light by the cornea are subject to the same chemical and mechanical influences as those which have been found for gelatin. Similarly, the anisotropy of the cornea is a function of its fibrous structure and lamellar arrangement. Its greatest swelling is at right angles to the direction of the axes of its fibers. The arrangement of the collagenous fibers in the fibrous tunic of the eye is believed to be fundamental in determining the optical difference between cornea and sclera.

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7. Dexter, E. O., and Kraemer, S. T.: The Light-Scattering Capacity (Tyndall Effect) and Colloidal Behavior of Gelatin Sols and Gels, *J. Phys. Chem.* **31**:764-782, 1927.

8. Gerngross, O.: Säurewirkung und  $H'$ -Konzentration bei Leim und Gelatine (unter besonderer Berücksichtigung der Trübungserscheinungen im isoelektrischen Punkt und der Gallertfestigkeit), *Kolloid-Beihefte* **40**:279-286, 1926.

9. Sheppard, S. E., and McNally, J. G.: The Structure of Gelatin Sols and Gels: II. The Anisotropy of Gelatin Gels, *Colloid Symposium Monographs*, Baltimore; Johns Hopkins Press, 1930, vol. 7, pp. 17-39.



# HYPERCALCEMIA AND BAND KERATOPATHY

Report of Nineteen Cases

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**A**BNORMALITIES in serum calcium values have only recently been recognized to have ocular manifestations. The first reported observation is that of Meesmann (1938).<sup>1</sup> In his study on hypocalcemia Meesmann included a case in which band-shaped opacities of the cornea and opacities of the conjunctiva developed while the blood calcium was high. The cause of the hypercalcemia was overdosage with AT 10® (dihydrotachysterol), which the patient had been taking for hypoparathyroidism following thyroidectomy. The patient also had glaucoma, and Meesmann stated the belief that the primary cause of the opacities was glaucomatous dystrophy of Bowman's membrane, but he suggested that the hypercalcemia might have been a contributing cause and pointed out significantly that the opacities became less as the blood calcium was reduced to normal. Haldimann (1941)<sup>2</sup> described band-shaped opacities of the cornea in 2 patients with sarcoid and hypercalcemia. In view of the fact that the opacities developed in 1 patient before other evidence of sarcoidosis of the eye and in the other patient without ocular sarcoidosis at any time, Haldimann suggested that the hypercalcemia alone might be the responsible factor.<sup>3</sup> Walsh and Howard (1947)<sup>4</sup> reported a series of 16 cases, including a preliminary report of 7 of our series, in which hypercalcemia from a variety of causes was associated with opacities of the cornea and conjunctiva in otherwise normal eyes. These authors pointed out

From the Howe Laboratory of Ophthalmology, Harvard Medical School; the Eye Service of the Massachusetts Eye and Ear Infirmary; the Department of Medicine of Harvard Medical School, and the Medical Service of the Massachusetts General Hospital.

1. Meesmann, A.: Hypokalzaemie und Linse; ein Beitrag zur Behandlung der Tetanie und der Cataracta tetanica mit AT 10 Holtz, *Klin. Monatsbl. f. Augenh. (supp.)* **100**:1-66, 1938.

2. Haldimann, C.: Hornhaut- und Bindehautveränderungen bei Boeckscher Krankheit, *Ophthalmologica* **102**:137-145, 1941.

3. The systemic aspects presented by these 2 patients have been discussed elsewhere (Schupbach, A., and Wernly, M.: Hyperkalcämie und Organverkalkungen bei Boeckschen Krankheit, *Acta. Med. Scandinav.* **115**:401, 1943).

4. Walsh, F. B., and Howard, J. E.: Conjunctival and Corneal Lesions in Hypercalcemia, *J. Clin. Endocrinol.* **7**:644-652, 1947.

that conjunctival opacities also occur characteristically in association with hypercalcemia but that there was no correlation of the blood calcium level with either the corneal or the conjunctival opacities. Frost, Sunderman and Leopold<sup>5</sup> reported an additional case of calcific deposits in the cornea and conjunctiva resulting from prolonged overdosage with vitamin D. It is the purpose of the present report to describe our 19 cases (including the 7 previously incorporated in the report of Walsh and Howard<sup>4</sup>). This will make a total of 32 cases which have been reported to date. The importance of the subject is not great from the point of view of local functional disturbances produced by the opacities, since these rarely encroach on the pupillary area, but the findings do have correlative value in the diagnosis of systemic disturbances of calcium metabolism and may indicate what is taking place in the kidneys. Moreover, the fact that in hypercalcemia, calcium precipitates in the eye and has a characteristic distribution in the eye has interesting physiologic implications.

The ocular findings to be reported consist of subconjunctival opacities, variously described as white flecks or as glasslike crystals, and corneal changes, consisting of a diffuse superficial opacity in the palpebral fissure with a limbal margin that is usually abrupt and concentric with the limbus but is separated from it by a clear interval. The axial margin, on the other hand, fades away gradually a few millimeters centralward. The corneal changes are those generally called band keratitis, but, for obvious reasons, are more properly designated as band keratopathy. While the conjunctival opacities might be confused with calcification of the conjunctiva which occurs commonly without definite local or systemic disease, the band opacities in the cornea can be readily distinguished from the white limbal girdle and other opacities which occur "normally."

## REPORT OF CASES

The following cases are grouped according to the etiologic factors in hypercalcemia.

### HYPERPARATHYROIDISM

CASE 1.—M. C., a housewife aged 41, who complained of multiple tumors and fractures of bones of three years' duration, was referred to the hospital with the diagnosis of hyperparathyroidism. Because of increased serum calcium, low serum inorganic phosphorus and characteristic changes in bone, she had undergone four operations, with removal of parathyroid tissue each time. Nevertheless, her symptoms continued, and she sustained her last fracture while en route to the hospital! There were no ocular symptoms. Roentgenograms showed a staghorn renal calculus on the right, generalized skeletal decalcification, bone cysts, absence of the lamina dura and pathologic fractures.

5. Frost, J. W.; Sunderman, F. W., and Leopold, I. S.: Prolonged Hypercalcemia and Metastatic Calcification of Sclera Following Use of Vitamin D in Treatment of Rheumatoid Arthritis, *Am. J. M. Sc.* **214**:585-592, 1947.

Laboratory analyses showed the following serum values: calcium, 15.4 mg.; inorganic phosphorus, 3.6 mg.; alkaline phosphatase, 20.6 to 26.5 Bodansky units; nonprotein nitrogen, 37 mg., and total protein, 6.1 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 2.6; carbon dioxide content, 22.5 to 24.4 milliequivalents. Urinalysis showed a negative to 3 plus reaction for albumin, 3 to 15 leukocytes and 0 to 40 red blood cells per cubic millimeter, abundant *Escherichia coli*, ability to concentrate to 1.016, 15 per cent excretion of phenol-sulfonphthalein in fifteen minutes and excretion of 359 to 445 mg. of calcium in twenty-four hours.

Examination of the eyes showed a superficial corneal opacity concentric with the limbus in the palpebral fissure. It was separated from the limbus by a clear interval and extended axialward, to fade out approximately 3 mm. from the limbus. Examination of the conjunctivas was inadequate, since the patient could not be studied with the slit lamp biomicroscope, but there was a reflex from the surface of the conjunctiva resembling that from massed fish eggs.

At a fifth operation, a carcinoma of the parathyroid with metastases to the lymph nodes was partially removed.

CASE 2.—P. G., a housewife aged 59, complained of generalized weakness, dyspnea, polyuria, polydipsia and swelling of the ankles. There were no ocular symptoms. Roentgenograms showed a ureteral stone, a duodenal ulcer and normal bony texture of the ribs and spine. Laboratory analyses showed the following serum values: calcium, 11.8 to 12.7 mg.; inorganic phosphorus 2.4 to 3.1 mg.; alkaline phosphatase, 1.6 Bodansky units, and nonprotein nitrogen, 23 mg., per hundred cubic centimeters; carbon dioxide content 23.8 to 28.1 volumes per cent. Urinalysis showed no albumin, an occasional leukocyte, inability to concentrate beyond 1.014 and 15 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed, in addition to unusually thin scleras, a superficial opacity on the nasal side of the cornea in the palpebral fissure, extending approximately 3 mm. from the limbus and separated from it by a thin, clear interval.

Adenoma of the parathyroid gland was removed at operation.

CASE 3.—N. T., a farmer aged 62, complained of polyuria, polydipsia and painless swelling of the left side of the maxilla. There were no ocular symptoms. Roentgenograms showed nephrocalcinosis, generalized skeletal decalcification and several bone cysts. Laboratory analyses showed the following serum values: calcium, 15.2 to 17.3 mg.; inorganic phosphorus, 2.4 to 3.7 mg.; alkaline phosphatase, 8 to 14 Bodansky units; nonprotein nitrogen, 31 to 45 mg., and total protein, 5.9 to 7.7 Gm., per hundred cubic centimeters; carbon dioxide content, 16.8 to 27.9 milliequivalents. The urine showed a negative to a 3 plus reaction for albumin, numerous leukocytes, abundant *Escherichia coli*, inability to concentrate beyond 1.015, no excretion of phenolsulfonphthalein in fifteen minutes and excretion of 560 mg. of calcium in twenty-four hours.

The eyes were examined for the first time ten weeks after the operation. At that time there were numerous white opacities in the superficial conjunctivas, most of which were less than 1 mm. in size and resembled a flocculent precipitate. They could be seen only with a slit lamp. There was no band keratopathy, and the eyes were otherwise normal.

Biopsy of the tumor of the maxilla revealed epulis. At a second operation an adenoma of the parathyroid was removed.

CASE 4.—E. K., a masseur aged 51, complained of tightness, stiffness and pain in the left calf. There were no ocular symptoms. A diagnosis of arteriosclerosis obliterans was made.

Twelve years previously he had been admitted with a diagnosis of hyperparathyroidism. Roentgenograms showed nephrocalcinosis and skeletal decalcification with bone cysts, two of which showed pathologic fractures. Laboratory analyses showed the following serum values: calcium, 16.8 mg.; inorganic phosphorus, 2.4 mg.; nonprotein nitrogen 32 mg., and total protein 5.7 Gm., per hundred cubic centimeters. Urinalysis showed 1 to 3 plus reaction for albumin, many leukocytes, an occasional red blood cell, *Esch. coli*, inability to concentrate beyond 1.018 and 5 to 15 per cent excretion of phenolsulfonphthalein in thirty minutes. An adenoma of the parathyroid was removed. The eyes were not examined at that time.

At the last admission laboratory analyses showed the following serum values: calcium, 11 mg.; inorganic phosphorus, 3.9 mg.; alkaline phosphatase, 3.9 Bodansky units; nonprotein nitrogen, 29 mg.; total protein, 6.7 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 2; carbon dioxide content, 29.7 milliequivalents. The urine showed no albumin, 3 to 20 leukocytes per cubic millimeter and *Esch. coli*.

TABLE 1.—*Data on Patients with Hyperparathyroidism*

Patient No.	Sex	Age	Present Complaint	Laboratory Data, Mg. or Units/100 Cc.			Non-protein Nitrogen	Urinary Calcium		Roentgenographic Findings	Duodenal Ulcer	Comment
				Calcium	Phosphorus	Phosphatase		Amount, Mg./24 hr.	Stone			
1	F	41	Multiple fractures	15.4	3.6	20.6-26.5	37	339-445	+	Marked decalcification; bone cysts; fractures	—	Carcinoma of parathyroid
2	F	59	Weakness and polyuria	11.8-12.7	2.4-3.1	1.6	23	.....	+	No decalcification (ribs and spine)	+	Adenoma of parathyroid
3	M	62	Epulis	15.2-17.3	2.4-3.7	8-14	31-45	560	+	Marked decalcification; epulis	..	Adenoma of parathyroid
4*	M	39	Multiple fractures	16.8	2.4	4.8-16.5	32	.....	+	Marked decalcification; bone cysts	—	Adenoma of parathyroid

\* Data in table are those obtained prior to removal of the adenoma of the parathyroid, that is, twelve years prior to the present examination.

Examination of the eyes showed an arcuate gray opacity at the nasal periphery of the cornea. This was superficial, was concentric with the limbus, from which it was separated by a clear interval, and faded out gradually 1 to 2 mm. from the limbus. The changes in the eyes were slight but otherwise typical of band keratopathy. There was only one opacity of the conjunctiva, over the region of the external rectus muscle.

Of this series of 4 cases in which the cause of the hypercalcemia was hyperparathyroidism, band keratopathy with conjunctival deposits was present in 2, band keratopathy alone in 1 and conjunctival deposits alone in 1. One of the patients had carcinoma of the parathyroid with extension to the lymph nodes. The other patients had adenomas of the parathyroid, removed at operation.

The pertinent data in these 4 cases are summarized in table 1. From the diagnostic point of view the important findings were as follows: increased serum calcium, depressed or normal serum

inorganic phosphorus, elevation of phosphatase and characteristic decalcification of the bones, with cyst formation in 3 of the cases. But most interesting is the occurrence in all of either nephrocalcinosis or nephrolithiasis, for, as will be discussed subsequently in consideration of the pathogenesis of band keratopathy, the mechanism by which calcification occurs in the cornea may be similar to that by which it occurs in the renal tubules; indeed, one of the most important practical consequences of band keratopathy may be its implications regarding the presence of similar changes in the kidneys. Also noted in table 1 is the occurrence in some of the patients of duodenal ulcer, for, as will be indicated in some types of hypercalcemia, the coexistence of ulcer with the high calcium, high alkali diet appears to be of significance.

#### VITAMIN D POISONING

CASE 5.—F. A., an engineer aged 27, complained of polydipsia and polyuria. For six years he had undergone extensive irradiation for generalized Hodgkin's disease. For four years he had taken 500,000 units of vitamin D a week for pruritus. The only ocular complaints were slight photophobia and burning of the eyes. Roentgenograms showed areas of increased density in the skull, spine and pelvis and miliary tuberculosis of the lungs. Laboratory analyses revealed the following serum values: calcium, 12.6 mg.; inorganic phosphorus, 4.3 mg.; alkaline phosphatase, 1.9 Bodansky units; nonprotein nitrogen, 52 mg.; total protein, 5.6 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.5; carbon dioxide content, 30.5 milliequivalents. The urine showed a negative to 1 plus reaction for albumin, 5 to 40 leukocytes and 0 to 4 red blood cells per cubic millimeter, cocci, ability to concentrate to 1.016, 15 per cent excretion of phenolsulfonphthalein in thirty minutes and excretion of 1,290 mg. of calcium in twenty-four hours.

Examination of the eyes showed a typical band keratopathy, symmetric in the two eyes, which extended approximately 3 mm. from the limbus on both the nasal and the temporal side. It was visible to the unaided eye.

The patient died, and autopsy revealed nephrocalcinosis, miliary tuberculosis and Hodgkin's lymphoma.

CASE 6.—E. B., a housewife aged 39, complained of abdominal pain, nausea, vomiting and swelling of the joints. For five years she had taken 100,000 units of vitamin D daily for rheumatoid arthritis. Roentgenograms showed a duodenal ulcer, extensive decalcification of the bones about the joints, periarticular calcification of soft tissues and no excretion of radiopaque dye in one hundred and five minutes. Laboratory analyses showed the following serum values: calcium, 10.2 to 14.4 mg.; inorganic phosphorus, 4.8 to 6.3 mg.; alkaline phosphatase, 3.3 to 7.4 Bodansky units; nonprotein nitrogen, 50 to 70 mg.; total protein, 7.0 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.15; carbon dioxide content, 21.4 to 24.9 milliequivalents. The urine showed a 4 plus reaction for albumin, 2 to 15 leukocytes per cubic millimeter, no organisms, inability to concentrate above 1.016, no excretion of phenolsulfonphthalein in fifteen minutes and excretion of 110 mg. of calcium in twenty-four hours.

Examination of the eyes showed superficial corneal opacities concentric with, but separated from, the limbus in the palpebral fissures, extending axialward about 3 mm. The conjunctivas also showed numerous fine opacities (presumably calcific) beneath the epithelium.

CASE 7.—A. M., a woman aged 70, complained of nausea, vomiting, diarrhea and depression. From eight to two months prior to admission she had taken 150,000 units of vitamin D daily for rheumatoid arthritis, from which she had suffered for fifteen years. She had consumed large amounts of milk. There were no ocular symptoms. Laboratory analyses revealed the following serum values: calcium, 11.7 to 13.9 mg.; inorganic phosphorus, 4.3 to 5.3 mg.; alkaline phosphatase, 4.0 Bodansky units; nonprotein nitrogen, 41 to 66 mg.; total protein, 7.5 to 8.2 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.1; carbon dioxide content, 21.4 milliequivalents. The urine showed a 1 to 3 plus reaction for albumin, 0 to many leukocytes and 0 to 30 red blood cells per cubic millimeter, no organisms, ability to concentrate to 1.017, 1 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 160 mg. of calcium in twenty-four hours.

Examination of the eyes without the aid of a slit lamp showed a definite band type of opacity in the palpebral fissure extending to 2 or 3 mm. from the limbus. No abnormality of the conjunctiva was to be seen grossly.



Photograph of the right eye of the patient in case 8. The paralimbal opacities can be seen as densest in the palpebral fissure and are characterized by an abrupt peripheral margin, bordering on a clear zone which separates it from the limbus and an axial margin fading out centrally 2 to 3 mm. from the limbus.

CASE 8.—T. C., a postal clerk aged 65, complained of vomiting and nocturia. For the past two to three years he had taken up to 300,000 units of vitamin D daily for rheumatoid arthritis. He consumed large quantities of milk. Recently several painless lumps had appeared in the skin of the neck, hands and wrists. The only ocular complaint was a mild foreign body sensation. Roentgenograms showed dense bones; calcification of soft tissues about the elbows, wrists and back, and rheumatoid arthritis. Laboratory analyses showed the following serum values: calcium, 11.6 to 15.2 mg.; inorganic phosphorus, 4.3 to 5.2 mg.; alkaline phosphatase, 4.4 Bodansky units; nonprotein nitrogen, 45 mg.; total protein, 7.32 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.25. The urine showed a negative to a 3 plus reaction for albumin, 0 to 30 leukocytes and 0 to 3 red blood cells per cubic millimeter, *Staphylococcus albus*, inability

to concentrate above 1.012, 5 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 445 mg. of calcium in twenty-four hours.

Examination of the eyes showed a typical band type of superficial opacities in the palpebral fissure of both corneas, the band being separated from the limbus by a narrow, clear interval and extending axialward 3 to 4 mm. (figure). While the opacities were densest between 8 and 10 o'clock and 5 and 2 o'clock, some of the opacity extended down to 6 o'clock but none up to 12 o'clock. The peripheral portions of the opacity had many clear lacunas, presumably in areas corresponding to portions of the opacity which had sloughed off. The conjunctivas showed a follicular reflex from their surface temporal to the limbus, and with the biomicroscope there were several subepithelial crystalloid opacities.

CASE 9.—P. A., a woman aged 55, complained of "lumps" about various joints. There were no ocular symptoms. From four to one and a half months prior

TABLE 2.—Data on Patients with Vitamin D Poisoning

Patient No., Sex, Age	Present Complaint	Laboratory Data, Mg. or Units/100 Cc.				Urinary Calcium		Roentgenographic Findings	Duodenal Ulcer	Dose of Vitamin D, Units/Day	Comment
		Calcium	Phosphorus	Phosphatase	Non-protein Nitrogen	Amount, Mg./24 Hr.	Stone				
5 M 27	Polydipsia; polyuria; pruritus	12.6	4.3	1.9	52	1,290	+	Increased density of spine, pelvis and skull	..	500,000 for 4 yr.	Tuberculosis; Hodgkin's disease
6 F 39	Epigastric pain	10.2-14.4	4.8-5.1	3.3	36-70	...	—	Metastatic calcification	+	100,000 for 5 yr.	Rheumatoid arthritis
7 F 70	Nausea; diarrhea; depression	11.7-13.9	4.3-5.3	4.0	80	160	—	Slight decalcification	..	150,000 for 6 mo.	Rheumatoid arthritis
8 M 65	Vomiting; nocturia	11.6-15.2	4.3-5.2	4.4	45	445	..	Excessive calcification in bone; metastatic calcification in skin	..	300,000 for 2-3 yr.	Rheumatoid arthritis
9 F 54	"Lumps" in soft tissues	13.4	5.7	5.9	62	125	—	Metastatic calcification in soft tissues	—	300,000 for 2½ mo.	Rheumatoid arthritis

to admission she had taken 300,000 units of vitamin D daily for rheumatoid arthritis, from which she had suffered for fourteen years. She had drunk 1 to 2 quarts (1 to 2 liters) of milk daily for several years. Painless lumps had appeared over one shoulder, both wrists and several fingers soon after she had started the vitamin D therapy. Roentgenograms showed normal bony texture; calcification of soft tissues about the hands, shoulders, back and knees, and rheumatoid arthritis. Laboratory analyses showed the following serum values: calcium, 13.4 mg.; inorganic phosphorus, 5.7 mg.; alkaline phosphatase, 5.9 Bodansky units; nonprotein nitrogen 62 mg.; total protein, 6.24 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 2.22; carbon dioxide content, 26.6 milliequivalents. The urine showed a 2 plus reaction for albumin, 0 to 3 leukocytes and 0 to 12 red blood cells per cubic millimeter, inability to concentrate above 1.010, less than 5 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 125 mg. of calcium in twenty-four hours.

Examination of the eyes showed bilateral and symmetric opacification of the nasal and temporal portions of the paralimbal cornea in the palpebral fissure.

These opacities were superficial, were separated from the limbus by a relatively clear zone and did not extend more than 2 to 3 mm. axialward.

In this series of 5 patients with hypercalcemia and band keratopathy, 4 had taken excessive vitamin D on account of rheumatoid arthritis and 1 had taken it for pruritus. The dose of vitamin D varied from 100,000 to 500,000 units daily, and the time over which the vitamin was taken varied from two and a half months to five years. All the patients had renal insufficiency, as indicated by the nonprotein nitrogen and inorganic phosphorus levels of the blood, but it is noteworthy that the diagnosis of nephrocalcinosis was not evident roentgenographically, but was made only at autopsy on the 1 patient who died. It is entirely possible, therefore, that nephrocalcinosis was present in the other patients.

In contrast to the series of patients with hyperparathyroidism, those with excessive vitamin D intake showed no characteristic decalcification of the bones and no significant elevation in the serum phosphatase level.

#### SARCOID

CASE 10.—F. L., an engineer aged 25, complained of shortness of breath, loss of weight and productive cough. The only ocular symptoms were mild redness of the eyes and a feeling of dryness for the preceding several weeks. The patient's occupation had entailed exposure to beryllium silicate powder. Roentgenograms showed sarcoidosis of the lungs and increased density of the spine. Laboratory analyses showed the following serum values: calcium, 11.3 to 15.6 mg.; inorganic phosphorus, 3.0 to 3.6 mg.; alkaline phosphatase, 6.7 to 8.4 Bodansky units; nonprotein nitrogen, 26 mg., and total protein, 6.7 to 7.1 Gm., per hundred cubic centimeters. The urine showed a negative to a 1 plus reaction for albumin, 0 to 3 leukocytes per cubic millimeter, ability to concentrate to 1.020 and 40 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed slight ciliary and conjunctival redness. The corneas showed grossly an arcuate opacity of the cornea concentric with the limbus but separated from it by approximately 1 mm. The opacity was predominantly in the palpebral fissure but involved the lower portion of the cornea as well. With the slit lamp this opacity appeared entirely superficial and faded out axialward approximately 3 mm. from the limbus. On the scleral side of the limbus numerous superficial white lines radiated from the limbus but did not extend more than 1 to 2 mm.

CASE 11.—A. M., a housewife aged 36, complained of shortness of breath and cachexia. There were no ocular symptoms. Roentgenograms showed sarcoidosis of the lungs, renal stones, slight skeletal decalcifications and a fusiform area of calcification in the left buttock. Laboratory analyses showed the following serum values: calcium, 13.0 to 15.5 mg.; inorganic phosphorus, 2.9 to 3.8 Bodansky units; nonprotein nitrogen 26.5 to 75 mg.; total protein, 8.7 to 9.5 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 0.7; carbon dioxide content, 28.9 milliequivalents. The urine showed a 2 to 3 plus reaction for albumin, 5 to many leukocytes and 1 to 10 red blood cells per cubic millimeter, no organisms, ability to concentrate to 1.020, 10 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 433 mg. of calcium in twenty-four hours.



Examination of the eyes showed band keratopathy in both eyes, more pronounced on the nasal than on the temporal side. In addition to the diffuse granular opacities, the band contained several tiny opaque loops, simulating the configuration produced by obliterated vessels.

Biopsy of a lymph node, removed at operation, showed Boeck's sarcoid.

The patient returned seven years later. Laboratory analyses of the serum revealed calcium, 10.0 mg; inorganic phosphorus, 3.0 mg., and nonprotein nitrogen, 24 mg., per hundred cubic centimeters.

Examination of the eyes showed considerable reduction in the band keratopathy, with practically no residuum nasally and only a 1 mm. band temporally. There were, however, numerous subepithelial opacities of the conjunctivas adjacent to the temporal limbus.

The association of sarcoid with beryllium poisoning has been noted several times in the literature, and the first of these 2 cases has been previously included in a series illustrating this association.<sup>6</sup>

TABLE 3.—*Data on Patients with Sarcoidosis*

Patient No., Sex, Age	Present Complaint	Laboratory Data, Mg. or Units/100 Cc.						Urinary Calcium		Roentgenographic Findings	Duodenal Ulcer	Comment
		Calcium	Phosphorus	Phosphatase	Non-protein Nitrogen	Protein	A/G	Amount, Mg./24 Hr.	Stone			
10 M 25	Shortness of breath and loss of weight	11.3-15.6	3.0-3.6	6.7-8.4	26	6.7-7.1	...	...	—	Increased density of spine	—	Sarcoidosis secondary to beryllium poisoning
11 F 36	Cachexia	13.0-15.5	2.9-3.8	2.9-3.7	26.5-75	8.7-915	0.7	433	+	Mild decalcification	—	Metastatic calcification in buttocks

One patient in this group showed impairment of renal function, as judged by the elevation of the nonprotein nitrogen and inorganic phosphorus levels of the blood, and at least 1 had nephrolithiasis. The changes in the kidneys and eyes, therefore, are similar to those resulting from excessive vitamin D intake.

#### UREMIA

CASE 12.—C. M., a clerk aged 49, complained of epigastric pain and shortness of breath. Five years previously he had had a sympathectomy for Buerger's disease (thromboangiitis obliterans). For twenty-five years he had taken large amounts of milk and alkali for relief of a duodenal ulcer. Roentgenograms showed a duodenal ulcer and normal bony texture. Laboratory analyses showed the following serum values: calcium, 11.4 to 12.8 mg.; inorganic phosphorus, 3.5 to 6.6 mg.; alkaline phosphatase, 2.2 to 3.1 Bodansky units; nonprotein nitrogen, 53 to 95 mg; total protein 6.81 Gm., per hundred cubic centimeters, with an

6. Hardy, H. L.: New Clinical Syndrome: Delayed Chemical Pneumonitis Occurring in Workers Exposed to Beryllium Compounds, *Bull. New England M. Center* 9:16-24, 1947.

albumin-globulin ratio of 1.8; carbon dioxide content, 35.3 milliequivalents. The urine showed a 2 plus reaction for albumin, a few leukocytes, rare red blood cells, hyaline casts, inability to concentrate beyond 1.012, 7 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 109 mg. of calcium in twenty-four hours.

Examination of the eyes showed superficial opacities on the nasal and temporal sides of both corneas, of symmetric distribution in the two eyes. The opacity was chalk white and was densest toward the limbus, where it was slightly elevated and contained clear lacunas. It was separated from the limbus by a narrow, clear zone and faded off gradually axialward about 3 mm. from the limbus. It was more pronounced nasally than temporally. There were a few crystalloid, superficial opacities in the perilimbal conjunctiva and a follicular reflex from the conjunctiva in the palpebral fissure resembling that from massed fish eggs. Examination sixteen months later, showed that the ocular condition was unchanged.

CASE 13.—A. C., a student aged 25, complained of protracted vomiting and emaciation. He had noted mild burning of the eyes. Roentgenograms showed periosteal formation of new bone; metastatic calcification in the tentorium, falx and bronchi, and small kidneys. There was no evidence of duodenal ulcer. Laboratory analyses showed the following serum values: calcium, 11.2 to 12.5 mg.; inorganic phosphorus, 4.4 to 4.8 mg.; alkaline phosphatase, 1.1 to 6.8 Bodansky units; nonprotein nitrogen 40 to 85 mg.; total protein 7.2 Gm., per hundred cubic centimeters; carbon dioxide-combining power 24.1 to 30.2 milliequivalents. The urine showed a 2 to 3 plus reaction for albumin, 0 to 6 leukocytes per cubic millimeter, inability to concentrate beyond 1.012 and 1 per cent excretion of phenolsulfonphthalein in twenty-four hours.

Examination of the eyes showed an abortive band type of corneal opacity concentric with the temporal limbus in the palpebral fissure. The adjacent conjunctiva was somewhat elevated and red and contained several subepithelial opacities.

The patient died three years later, without presenting further evidence of the fundamental cause of his disease.

CASE 14.—V. Z., a housewife aged 23, complained of anorexia, nausea, vomiting, polydipsia and polyuria. She had avoided use of milk and alkalis. There were no ocular symptoms. The blood pressure was 190 systolic and 100 diastolic. Roentgenograms showed two calculi in the left ureter, slight decalcification of the spine, a normal lamina dura and poor renal excretion of radiopaque dye on the right and none on the left. Laboratory analyses showed the following serum values: calcium 13.2 to 13.4 mg.; inorganic phosphorus, 3.8 to 4.6 mg.; alkaline phosphatase, 1.8 to 2.6 Bodansky units, and nonprotein nitrogen, 40 to 45 mg., per hundred cubic centimeters; carbon dioxide content, 30 milliequivalents. The urine showed no albumin, a few leukocytes and red blood cells, a few alpha hemolytic streptococci, inability to concentrate above 1.012, excretion of 15 per cent of phenolsulfonphthalein in fifteen minutes and excretion of 187 to 413 mg. of calcium in twenty-four hours.

Examination of the eyes showed narrow bands of a superficial white opacity of irregular lacelike character situated on both the nasal and the temporal portion of the cornea of both eyes in the palpebral fissure. There were also many superficial irregular white opacities in the conjunctiva beneath the epithelium, but overlying the blood vessels.

Biopsy of two parathyroid glands showed secondary hyperplasia.

CASE 15.—A. M., a gardner aged 45, complained of weakness, nocturia and polydipsia. He had taken large amounts of milk and alkali for relief of a duodenal ulcer, from which he had suffered for many years. Five years previously he had passed renal calculi. For the past three years he had noted mild redness of the eyes. Roentgenograms showed renal stones, a duodenal ulcer and normal bony texture. Laboratory analyses showed the following serum values: calcium, 14.6 to 7.7 mg.; inorganic phosphorus, 4.0 to 9.4 mg.; alkaline phosphatase, 1.7 to 5.3 Bodansky units; nonprotein nitrogen 58 to 83 mg.; total protein 9.1 to 9.8 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.8; carbon dioxide content, 27.4 to 31.1 milliequivalents. The urine showed 2 to 40 leukocytes and 0 to 3 red blood cells per cubic millimeter, no organisms, inability to concentrate beyond 1.010, and 5 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed symmetric changes in the palpebral fissures in the corneas, consisting of slightly elevated white opacities concentric with the limbus, from which they were separated only by relative thinning, and extending axialward 2 to 3 mm., where they became nonelevated and apparently subepithelial. The opacities were situated on both the nasal and the temporal side of the corneas and were thought to be typical of band keratopathy. There were also yellowish and irregular plaques, measuring 4 to 5 mm. in diameter, situated, one each, in the nasal and temporal episcleras of both eyes. An attempt was made to remove one of these plaques for biopsy, but it was too firmly attached to the sclera and was left in situ.

The patient was kept under observation until he died in uremia six years later, during which time no evident change took place in his eyes.

Biopsy of two parathyroid glands, removed at operation, revealed a normal structure.

Autopsy showed nephrocalcinosis and calcification of the dura mater, respiratory diaphragm, costal cartilages, tendons and blood vessels.

CASE 16.—E. F., a stenographer aged 48, complained of pruritus and weakness. There were no ocular symptoms. Roentgenograms showed skeletal decalcification with bone cysts, osteoarthritis, a calcified deposit near the right elbow and contracted kidneys. Laboratory analyses showed the following serum values: calcium 8.8 mg.; inorganic phosphorus, 8.9 to 10.1 mg.; nonprotein nitrogen 140 to 155 mg.; total protein, 6.6 to 6.7 Gm., per hundred cubic centimeters, with an albumin-globulin ratio of 1.35; carbon dioxide content, 21.7 milliequivalents. The urine showed a 1 to 2 plus reaction for albumin, few leukocytes and red blood cells, no organisms, inability to concentrate beyond 1.012 and 5 per cent excretion of phenolsulfonphthalein in fifteen minutes.

Examination of the eyes showed a superficial opacity of each cornea on the nasal and temporal sides in the palpebral fissure, extending from the limbus approximately 2 mm. axialward, where it gradually faded out. No definite clear zone separated it from the limbus. Numerous tiny opacities also were situated just beneath the epithelium of the conjunctiva in the palpebral zone. These were placed superficial to the blood vessels and moved with blinking of the lids.

The patient died a few months later, without further examination.

CASE 17.—J. L., a fireman aged 52, complained of hematemesis. For many years he had taken large amounts of milk and alkali for relief of a duodenal ulcer.

Three years previously he had been admitted to the hospital with the complaint of a painful right eye. He stated he had had a "cataract operation" on the right eye as a child and that the vision had subsequently been poor. On this admission the following note was made: "Right eye was red, and practically the

entire cornea was infiltrated with calcium deposits. There was moderate ectasia. The chamber was deep. The pupil was small and immobile. The fundus reflex was absent. Tension was 3 plus. The left eye showed moderate but diffuse conjunctival redness and a marginal corneal opacity temporally and nasally from 2 to 5 o'clock and from 10 to 7 o'clock. The chamber, pupil and tension were normal." Because the glaucoma in the right eye was not relieved by miotics and the pain persisted, the eye was enucleated. Histologic examination of the cornea showed that the stroma and the posterior surface were not abnormal. Bowman's membrane was intact and appeared normal in its axial portion for an extent of 4 mm., but became increasingly calcified toward the periphery. At its limbal extremity the calcification of Bowman's membrane was densest and extended into the superficial stroma. Anterior to Bowman's membrane, and separated from it by a clear interval (an artefact), there was a new-formed membrane of lamellar stratification having a thickness about one-third that of the entire stroma. This new-formed membrane was composed for the most part of connective tissue with a variable amount of collagen and variable amount of hyalinization. At its periphery the membrane contained epithelium, which in the sections was not connected with the surface epithelium. In the anterior part of this new-formed membrane were calcific plaques, some of which were erupting through to the surface. These, like the calcification in Bowman's membrane, were more conspicuous toward the periphery of the cornea, where they could be seen extending through the whole thickness of the membrane. Also noteworthy were areas of calcification of the superficial half of the sclera in the region overlying the ciliary body. This was about 2 mm. in length on one side and involved one-half the thickness of the sclera and an area about 1 mm. in length on the other side and involved one-fourth the thickness of the sclera.

At the time of the present examination, roentgenograms revealed a duodenal ulcer, normal bony texture and no excretion of the radiopaque dye in forty-five minutes. Laboratory analyses showed the following serum values: calcium, 11.4 mg.; inorganic phosphorus, 4.7 mg.; alkaline phosphatase, 5.3 Bodansky units; nonprotein nitrogen, 80 to 105 mg.; total protein 6.8 Gm., per hundred cubic centimeters; carbon dioxide content, 21.8 milliequivalents. The urine showed a negative to a 1 plus reaction for albumin and inability to concentrate beyond 1.010.

Examination of the left eye showed a typical band-shaped opacity of the cornea in the palpebral fissure extending on the nasal and temporal sides from the limbal margin approximately 3 mm. axialward. The limbal edge of the opacity was irregularly scalloped and slightly raised, showing clear lacunas corresponding to portions of the opacity which had presumably been sloughed off. The opacity was entirely superficial. The conjunctiva showed grossly a follicular type of reflex in a 3 mm. zone temporal to the limbus and examination with the slit lamp biomicroscope revealed several subepithelial crystalloid opacities.

CASE 18.—E. M.,<sup>7</sup> a carpenter aged 55, complained of nocturia, pruritus and swelling of the legs. For twenty one months he had taken daily 4 to 5 quarts (4 to 5 liters) of milk and considerable alkali for relief of a duodenal ulcer. Physical examination showed movable subcutaneous nodules of the forearms. Roentgenograms showed calcification of the soft tissues of the extremities, and clubbing of the calyces was evident in retrograde pyelograms. Laboratory analysis showed the following serum values: calcium, 9.6 to 13.0 mg.; inorganic phosphorus, 3.7 to 5.9 mg.; alkaline phosphatase, 3.2 to 4.5 Bodansky units; nonprotein nitrogen,

7. Dr. Charles Burnett, of the Massachusetts Memorial Hospital, 65 East Newton Street, Boston 18, furnished the data on this patient.

80 to 100 mg.; total protein, 6.8 to 8.2 Gm., per hundred cubic centimeters; carbon dioxide-combining power, 24.0 milliequivalents. The urine showed a 1 to 2 plus reaction for albumin, occasional leukocytes and red blood cells, inability to concentrate beyond 1.011, less than 1 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 78 mg. of calcium in twenty-four hours.

Examination of the eyes showed a superficial opacity of the cornea in the paralimbal region of the palpebral fissure. It was present on both the nasal

TABLE 4.—Data on Patients with Uremia

Patient No.	Sex	Age	Present Complaint	Laboratory Data, Mg. or Units/100 Cc.				Non-protein Nitrogen	Urinary Calcium		Roentgenographic Findings	Duodenal Ulcer	Comment
				Calcium	Phosphorus	Phosphatase			Amount, Mg / 24 Hr	Stone			
12	M	49	Epigastric pain	11.4 12.8	3 5-6 6	2 2-3.1		53 95	109	.	No decalcification	+	Intermittent claudication, much alkali and milk in diet
13	M	25	Vomiting 2½ yr.	11 2-12 5	4 4 4 8	1.1 6 8		40-85	. . . .	..	Calcification in bronchi and dura; periosteal new bone	—	Patient died; hyperparathyroidism not excluded
14	F	23	Vomiting, anorexia; polydipsia; polyuria	12 2 13 4	3 6-4 6	1.8 2 6		40-45	187 413	+	Mild decalcification	—	Two operations on parathyroid region showed secondary hyperplasia only
15	M	45	Weakness, nocturia; polydipsia	14 6 7.7	4 0-9 4	1 7 5 3		58 171		+	No decalcification	+	Much alkali and milk in diet, no parathyroid adenoma found surgically or post mortem
16	F	48	Pruritus; weakness	8 8	8 9 10 1	. . .		140 155		—	Marked decalcification	..	Patient died a few months later
17	M	52	Hematemesis	8 3 11 4	3 9 4 7	4 4 5 3		65-109		—	No decalcification	+	Much alkali and milk in diet
18	M	55	Nocturia; edema	9 6 13 0	3 7 5 9	3 2 4 5		80 100	78	—	Metastatic calcification in soft tissues	+	Much alkali and milk in diet
19	M	75	Urinary frequency	11 5 13 4	4 1 5 4	11 7-14 1		35-37	250-495	—	Ostitis deformans (Paget's disease)	.	Much milk in diet; hyperparathyroidism not excluded

and the temporal side, was about 4 mm in length, was separated from the limbus by a narrow, clear interval and extended axialward about 2 mm. There were also scattered translucent bodies superficial in the conjunctiva extending 6 to 7 mm. temporal to the limbus and a few similar bodies extending nasalward.

CASE 19.—B. S., a fireman aged 75, complained of urinary frequency. For over a year he had taken daily 3 capsules containing a white powder. For several months he had taken 2 quarts (2 liters) of milk a day. There were no ocular symptoms. Roentgenograms showed generalized Paget's disease (ostitis de-

mans) and good renal excretion of radiopaque dye. Laboratory analyses showed the following serum values: calcium, 11.5 to 13.4 mg.; inorganic phosphorus, 4.1 to 5.4 mg.; alkaline phosphatase, 11.7 to 14.1 Bodansky units; nonprotein nitrogen, 35 to 37 mg.; total protein, 6.1 Gm., per hundred cubic centimeters; carbon dioxide content, 30.6 milliequivalents. The urine showed a negative to a 2 plus reaction for albumin, 0 to 8 leukocytes and 0 to 3 red blood cells per cubic millimeter, no organisms, inability to concentrate beyond 1.010, 15 per cent excretion of phenolsulfonphthalein in fifteen minutes and excretion of 250 to 495 mg. of calcium in twenty-four hours.

Examination of the eyes showed a typical band of keratopathy extending 2 to 3 mm. onto the cornea, without any definite clear zone separating it from the periphery. It was more pronounced on the temporal than on the nasal side. It was accompanied with three to four translucent crystals in the adjacent conjunctiva.

The cause of this patient's hypercalcemia and hyperphosphatemia with impaired renal function has not been determined. Differential diagnosis includes hyperparathyroidism, rapidly advancing osteitis deformans and the syndrome of Burnett and associates.<sup>8</sup>

From several points of view this group of cases is most interesting. They have in common uremia, band keratopathy and, with 1 exception, hypercalcemia. The etiologic factor was not apparent, but it is noteworthy that in at least 5 of them (cases 12, 15, 17, 18 and 19) high milk and high alkali diets had been taken for some time and the cases fall under the syndrome described by Burnett and associates,<sup>8</sup> in which renal damage (nephrocalcinosis?) is believed to result from high calcium and alkali intake. In 2 other cases in the series (cases 13 and 14) there was prolonged vomiting, and a nephrocalcinosis secondary to the chronic alkalosis may similarly have developed. The pathogenesis of the band keratopathy would presumably be the same as that of the calcification of the kidneys.

With the development of sufficient renal damage, the serum non-protein nitrogen and inorganic phosphorus increase. But since the phosphorus and calcium levels of the blood tend to maintain reciprocal levels, the calcium which was originally abnormally high may fall to abnormally low levels as uremia supervenes. Thus, in case 15, when there was only moderate uremia, as indicated by serum non-protein nitrogen of 80 mg., the calcium was 14.6 mg. and the inorganic phosphorus 4.7 mg. per hundred cubic centimeters, but when, toward the terminal stage, the serum nonprotein nitrogen had risen to 171 mg. and the inorganic phosphorus to 9.4 mg. per hundred cubic centimeters the calcium had fallen to the abnormally low level of 4.7 mg. per hundred cubic centimeters. We are not prepared to state to what extent band keratopathy may occur with renal damage and rising serum

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8. Burnett, C. H.; Commons, R. R.; Albright, F., and Howard, J. E.: Hypercalcemia Without Hypercalcuria or Hypophosphatemia, Calcinosis and Renal Insufficiency: A Syndrome Following Prolonged Intake of Milk and Alkali, *New England J. Med.* **240**:787-794 (May 19) 1949.

inorganic phosphorus in cases in which there is not a preexisting hypercalcemia. Whereas the data on case 16 suggest that this change in the cornea may occur, the patient was first seen in the terminal stage of her disease, at a time when the serum nonprotein nitrogen and inorganic phosphorus levels were very high. The normal serum calcium may or may not have been preceded by a high level.

#### SUMMARY

Band keratopathy and calcification of the conjunctiva is reported in 18 cases of hypercalcemia and in another case in which the calcium level of the blood may be presumed to have been elevated previously. The hypercalcemia was due to hyperparathyroidism in 4 cases, to vitamin D poisoning in 5 cases and to sarcoidosis in 2 cases. In the remaining 8 cases it was associated with severe renal damage, owing, in some of the cases, to a high calcium and high alkali intake. The corneal opacity consisted of paralimbal opacification of the cornea extending 2 to 3 mm. axialward in the palpebral fissure. Many of the patients had nephrocalcinosis or nephrolithiasis, and the process occurring in the kidneys was thought to be analogous to that occurring in the cornea.

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# DERMOID AND EPIDERMOID TUMORS OF THE ORBIT

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**D**ERMOID and epidermoid tumors of the orbit are uncommon if the paraorbital growths or those located superficially in the eyelids are excluded. Of a series of 200 consecutive cases of exophthalmos reported in 1941 by one of us (R. L. P.),<sup>1</sup> instances of these congenital growths comprised 4 per cent. Constans<sup>2</sup> in 1943 collected from the literature 15 cases of cholesteatoma of the orbit and reported another; he stated that most of the tumors in his series should more correctly have been termed dermoids. Birch-Hirschfeld<sup>3</sup> in 1930 found 5 cases in the records of the Leipzig clinic. Samuels<sup>4</sup> in 1936, before this society, reported the histologic study of 13 dermoid cysts but failed to differentiate orbital from paraorbital growths. Many reports of isolated cases of oil, or dermoid, cysts affecting the orbit are to be found throughout the older and the more recent literature. When intra-orbital these growths displace the eyeball, and it is they which we desire to discuss; we shall report a series of 9 cases and call attention to the characteristic defects in the bone of the orbit which these tumors produce and which may usually be recognized by roentgenography.

## DIFFERENTIATION

Although the dermoid and the epidermoid are closely related in origin and behavior and require similar treatment, much has been

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1. Pfeiffer, R. L.: Roentgenography of Exophthalmos with Notes on Roentgen Ray in Ophthalmology, *Tr. Am. Ophth. Soc.*, **39**:492, 1941; *Am. J. Ophth.* **26**:724, 816, and 928, 1943.

2. Constans, G. M.: Cholesteatoma of Orbit, *Arch. Ophth.* **30**:236 (Aug.) 1943.

3. Birch-Hirschfeld, A.: Das Dermoid des Orbita, in Graefe, A., and Salmisch, T.: *Handbuch der gesamten Augenheilkunde*, Berlin, Julius Springer, 1930, p. 556.

4. Samuels, B.: Dermoid Cysts of the Orbit, *Arch. Ophth.* **16**:776 (Nov.) 1936.



written of their differentiation. The term epidermoid has replaced the older "cholesteatoma," or *tumeur perlée*<sup>5</sup> of the French, and is now in general use among neurologists, who have written most on the subject. The differentiation of dermoids from epidermoids seems academic. All the tumors are congenital rests from primitive ectoderm, and perhaps mesoderm as well, and the composition of each type depends simply on the time at which the cell rest developed, according to Boström,<sup>6</sup> or to the degree or depth of inclusion of the original dermal layer, according to Horrax.<sup>7</sup> Boström insisted that in the epidermoid growths all the tissue elements were derived from epithelial tissue. He regarded the dermoids, which contain mesoblastic structures, as arising from a dermis which differed not in actual depth of the original layer but in embryonic antiquity. A younger and more primitive cell layer, he suggested, will give rise to both epithelial and mesothelial tissues and the tumor will be characterized by a dermoid rather than an epidermoid type of growth. Both are primary epithelial tumors resulting from sealed inclusions, with the resulting structure depending on one of two factors. The depth of the primitive layer seems to be the critical factor, the epidermoid arising when the epidermoid tissue alone is concerned and the dermoid when the deeper, dermal, layer is in question. In either case, transitional types must and do occur commonly and make the differentiation unimportant. According to Critchley and Ferguson,<sup>8</sup> however, whose paper did most to clarify this subject, although there is little histologic or embryologic distinction between the dermoid and the epidermoid growths, there appear to be certain points of differentiation both clinically and anatomically. Thus, dermoid tumors produce symptoms earlier than do epidermoid tumors, are more likely to be multiple and often break down in the center to form cysts. In addition, the dermoid growth is more often associated with other congenital anomalies and developmental errors. These considerations assume little importance in the series of cases here reported. The ages of our patients ranged from 5 to 63 years, and the age distribution showed no significant relation to the type of growth except that the youngest patient had the only classic dermoid. All the

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5. Cruveilhier, J.: *Anatomie pathologique du corps humain, ou descriptions avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible*, Paris, J. B. Baillière, 1829, vol. 2, pt. 1, plate 6.

6. Boström, E.: Ueber die pialen Epidermoide, Dermoide, und Lipome und duralen Dermoide, *Centralbl. f. allg. Path. u. path. Anat.* **1**:1897.

7. Horrax, G.: A Consideration of the Dermal Versus the Epidermal Cholesteatomas Having Their Attachment in the Cerebral Envelopes, *Arch. Neurol. & Psychiat.* **8**:265 (Sept.) 1922.

8. Critchley, M., and Ferguson, F. R.: Cerebral-Spinal Epidermoid Cholesteatoma, *Brain* **51**:334, 1928.

tumors were single cystic lesions, unassociated with other known congenital anomalies.

*Dermoids.*—The orbital and intracranial dermoids vary from the size of a small seed to that of a large apple. They are encapsulated, are oval, round or hourglass in shape; their consistency is soft, usually cystic, and they are opaque, yellow or brownish, the color depending on the presence of hemosiderin. If the tumor is cystic, the content is fatty, soapy, flaky or crumbly. The presence of sebaceous material, fat and cholesterol crystals, in varying proportions, determines the consistency of the mass, and the tumor always contains hairs, coiled, clumped or matted together. The presence of hair has been regarded as pathognomonic of the dermoid. Boström, Horrax and others, however, have recorded cases of epidermoid cysts in which hair was found, and such growths may thus be regarded as transitional. A low grade inflammatory reaction was manifest in the walls of most dermoids.

Microscopically, the constituents of dermoid tissue resemble those of skin, and one can distinguish, from without inward, a fibrous, outer layer; a connective tissue stroma (corresponding to the corium), and an epithelial, inner layer. Blood vessels may be seen in the connective tissue layer, especially at the site of the dermoid tuft, which represents the location of the original dermal implantation and the place of greatest growth. In addition, this layer may contain sebaceous glands, hair follicles, fat cells, smooth muscle and elastic fibers. Deposits of calcium and cartilaginous spicules may also be seen in the connective tissue matrix.

The epithelial, inner layer, a purely ectodermal derivative, varies greatly in thickness, consisting sometimes of a single layer of cells and at others of a stratification similar to that of skin, with germinative, granular and cornified layers. As in normal skin in which there are a number of layers of cells, the innermost ones have the more flattened or polygonal cells, and in these layers the nuclei disappear, the cells become horny and keratohyalin bodies and cholesterol crystals (the end products of epithelial disintegration) occur.

In the main cavity of the dermoid cyst, varying amounts of hair, sebum, cholesterol and oil are present. This material may be rancid and toxic and may be irritating and produce evidence of inflammation in the cyst or in neighboring tissue. A tooth was found in Borley's<sup>9</sup> case. Samuels found the epithelial layer incomplete in some cysts and observed little tendency of the epithelium to proliferate in filling in defects. Such defects are found associated with the inflammatory reaction. He observed cellular and granulation tissue undermining the epithelium and, in the deeper layers of the wall, nodules of epithelioid

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9. Borley, W. E.: Dermoid (Oil) Cyst of Orbit, Am. J. Ophth. **22**:1355, 1939.

or giant cells. According to Samuels, the so-called oil cysts show a predominance of sebaceous glands. Vassaux and Broca<sup>10</sup> expressed the belief that the oil represented degenerated fat cells, but this statement is not borne out by chemical analysis and histologic observation. Knapp's<sup>11</sup> case, reported before this society, is noteworthy for the chemical examination of the content of the cyst. Jones<sup>12</sup> reported a case of an oil cyst which became malignant, the patient dying of carcinomatosis. It is probable that the so-called blood cysts are dermoid cysts in which hemorrhage has occurred and in which, because the entire cyst could not be examined, an epithelial lining was not found.

The histologic study of these large growths leaves much to be desired. Because of the technical difficulties at operation, only fragments of the wall of the cyst, along with some of the content, can be offered for study. Study of the smaller paraorbital dermoids is only indicative of the structure of these large growths, which have been subject to pressure influences from within and from without and to impoverished circulation, perhaps, with degeneration occurring within, forming toxic substances which react on the mother tissue. Most of the smaller paraorbital growths, with the solid mass of epithelial products within (often mistaken for sebaceous cysts), are good examples of epidermoid cysts).

*Epidermoid.*—This simpler tumor forms a solid mass which may be described as being made up of two concentric layers of different thicknesses, forming the capsule, and a main, central mass, making up the bulk of the tumor. The outer layer, or stratum durum, which gives the tumor its nacreous sheen, may be thin or so thick as to constitute a tough, fibrous envelope. It is composed of layers of collagen fibers, with little or without cellular formation. Beneath the stratum durum lies the characteristic layer, which constitutes the histologic criterion of the epidermoid cyst. The stratum granulosum, as it is called, is essentially a cellular layer of epithelial cells, which varies in thickness from one or two cells, as is usually the case, to ten or more layers of cells, the layers varying in character according to their depth. Fine granules composed of keratohyalin are scattered throughout the cytoplasm of these cells. The interior of the tumor is composed of the accumulated products of the desquamated epithelial layer, which appears in loosely packed layers of wavy, homogeneous laminae, with numerous flat cholesterol crystals. This tumor is completely avascular, and the content is nonvital.

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10. Vassaux, G., and Broca, A.: Contribution à l'étude des kystes à contenu huileux, Arch. d'ophth. 3:318, 1883.

11. Knapp, A.: Oil Cyst of Orbit, Arch. Ophth. 52:163 (March) 1923.

12. Jones, A. C.: Oil Cyst of Orbit with Carcinomatosis, Am. J. Ophth. 18: 532, 1935.

The nomenclature of the epidermoid tumors has caused considerable confusion. The term cholesteatoma is not applicable. Because cholesterol does not play an essential role in the histology of these growths and is found in a great variety of tumors, the use of this name should be discontinued. The indispensable criterion for the diagnosis of epidermoid growths is the microscopic demonstration of epidermoid elements making up the wall of the tumor. One is logically bound to name the growth from its essential feature, and the term suggested by Critchley and Ferguson, that is, epidermoid, should be used. But, in view of the close relation of this tumor to the dermoid, one may well question the propriety of making the distinction. The term dermoid seems adequate.

Something should be added to distinguish the congenital epidermoid cyst from the cholesteatoma associated with disease of the middle ear. The latter lesions, associated with infection of the middle ear cavity, consists mainly of epithelial debris with fat, granulation tissue, leukocytes and cholesterol crystals and may be simply the accumulated products of excessive desquamation and reaction to inflammation (cholesteatosis). Erdheim,<sup>13</sup> Lucae<sup>14</sup> and Kuhn,<sup>14</sup> however, reported typical epidermoid cysts in the middle ear unassociated with infection. It may be that under the stimulus of the inflammatory process the back-growth of the meatal epithelium through the tympanic cavity gives rise to dermoid formation. It is possible, on the other hand, that the tumor may be present in the middle ear as an epithelial rest and that its presence predisposes the ear to suppuration, so that infection and tumor formation are discovered in association with each other.

*Present Series.*—Most of the cases described here had characteristics of both the dermoid and the epidermoid. Only 1 tumor of our series contained hair (case 8). All the growths were cystic and contained a brown, oily fluid, with cholesterol and hemosiderin and sometimes masses of yellowish debris. All had fibrous walls, of variable character, with epithelial lining. In many cysts blood vessels were revealed at operation and on section. Low grade inflammatory reaction was manifest in the walls of most of the tumors.

In all but 1 of these cases (case 8) the tumors appeared to be intermediate or transitional types arising either from deep, or early, or from superficial, or late, epithelial rests. The oil content must be recognized as evidence of the presence of sebaceous glands, though these structures were not conspicuous in the walls of most of the tumors. The blood vessels attest to the depth of the layer and the presence of a mesodermal constituent in the original cell rest. The absence of

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13. Erdheim, J.: Ueber Schädelcholesteatoma, Ztschr. f. Ohrenh. **49**:281, 1905.

14. Cited by Critchley and Ferguson.<sup>8</sup>

hair, however, indicates the superficiality of the epithelial rest. The brown or chocolate color of most of the tumors was due to the hemosiderin content and indicated that bleeding had occurred, probably as a result of the toxicity of the content and the secondary inflammatory reaction, with rupture of vessel walls. The epithelial layer in all 8 cases was extremely thin, and the great masses of cholesterol were common to both types.

The case of Rasquin,<sup>15</sup> that of a multilocular dermoid of the orbit in which one portion was an oil cyst and another a solid epidermoid (though he called it a sebaceous cyst), is evidence of the relation of dermoid and epidermoid cysts.

We have encountered no reference in the literature to the possibility of epidermoids undergoing degeneration with liquefaction. It would seem that these tumors maintain their solid form, even though they reach massive proportions and are without blood vessels. Although a nonvitalized growth, they seem not to become toxic. The case of King<sup>16</sup> (case 4 in his series), in which a very large cyst involving the orbit was filled with thick, viscid, olive-green material of the consistency of coal tar, together with semifluid, opaque masses, most nearly suggests a combination of dermoid and epidermoid constituents. King attributed this odd situation, however, to a communication with the ethmoid and/or frontal sinuses. In none of our cases did the cysts communicate with the sinuses. The content of retention cysts, or mucocoeles, arising in a paranasal sinus is altogether different from that of a dermoid cyst and need not be confused.

#### ROENTGENOGRAPHY

The dermoids or epidermoids may arise in the diploe of the skull or bones of the orbit and in their growth expand both the inner and the outer table and produce rather characteristic defects. They may arise subperiosteally or subsuperiorbally and produce fossae or indentations of the bone with typical markings. These defects, whether fossae, dehiscences or openings in the bone, may be demonstrated roentgenographically and may serve to indicate the nature of the process and, in case of involvement of the orbit, the cause of the resulting exophthalmos.

In the older literature, defects in the bone of the orbit associated with dermoids discovered at operations were mentioned by Doyne,<sup>17</sup>

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15. Rasquin, E.: Kyste dermoïde multiloculaire interne de l'orbite à contenu huileux, *Bull. Soc. belge d'opht.* **64**:78-80, 1932.

16. King, J. E. J.: Extradural Diploic and Intradural Epidermoid Tumors (Cholesteatoma), *Ann. Surg.* **109**:649, 1939.

17. Doyne, R. W.: Dermoid Tumor of Orbit, *Ophth. Rev.* 1896, p. 97.

Chevallereau,<sup>18</sup> Cant<sup>19</sup> and Krönlein.<sup>20</sup> Since the discovery of the roentgen ray more frequent mention of orbital changes may be noted (Pincus,<sup>21</sup> Michail,<sup>22</sup> Varona,<sup>23</sup> Kreibig,<sup>24</sup> Panneton and Roux,<sup>25</sup> Constans<sup>2</sup>). No special attention had been given, however, to the bony defects as a possible means of diagnosing dermoid of the orbit. Our series of 9 cases, which comprises all the verified cases of dermoids and epidermoids which we have seen, may well illustrate the importance and nature of the bony involvement in the diagnosis and treatment of these growths. In addition, 5 more unmistakable cases have been studied, but have not as yet been verified histologically and are not considered in this paper.

In their most typical form, the defects in the bone of the orbit produced by these congenital growths are revealed in roentgenograms by sharply demarcated margins, with increase in the density of the bone at the margin, and diminished tissue density within the confines of the lesion itself. In the first case such studies revealed a bean-shaped fossa in the lateral wall of the orbit, and in the second case, a bean-shaped hiatus or dehiscence in the roof of the left orbit, with the features mentioned. The next 3 cases illustrate different stages in the development of dermoids in the roof of the orbit near the zygomatic process of the frontal bone. Case 6 demonstrates the startling size which one of these lesions may attain. This case is remarkable in the thickness and density of the bone in the wall of the cyst. The diminished soft tissue density and the increased radiolucency of the growth are due to the oil and/or cholesterol content. When associated with dehiscence of the bone, with calcium of the bone therefore lacking, the dark appearance of the growth is striking in the roentgenogram.

In the present series, the frontal bone was involved in 7 of the 9 cases. In 6 of these 7 cases the growth appeared to have arisen in the diploe of the bone forming the roof of the orbit. In cases 2 and 9 a through and through defect in the bone was produced, so that pulsation of the dura was observed at operation. An hourglass tumor

18. Chevallereau, A.: Kyste dermoïde à parois osseuses et à contenu pierreux, Soc. d'opht. **5**:1, 1892.

19. Cant, W. J.: Cyst of Orbit, Ophth. Rev. 1896, p. 187.

20. Krönlein, R. U.: Zur Pathologie und operativen Behandlung der Dermoidcysten der Orbita, Beitr. z. klin. Chir. **4**:149, 1889.

21. Pincus, F.: Ueber "Cholesteatom" der Orbita, Klin. Monatsbl. f. Augenh. **90**:145, 1933.

22. Michail, D.: Cholestéatome de l'orbite, Arch. d'opht. **48**:743, 1931.

23. Merino, Varona, A.: Presentación de un caso de colesteatoma de la órbita, Rev. de méd. y cir. de la Habana **42**:687, 1937.

24. Kreibig, W.: Zur Kenntnis seltener Orbitaltumoren, Ztschr. f. Augenh. **95**:113, 1938.

25. Panneton, P., and Roux, R.: Un cas très rare de cholesteatome de l'orbite, Union méd. du Canada **70**:812, 1941.

was found in case 7, with portions both in the frontal fossa and in the orbit. The largest tumor (case 6) appeared to have arisen in the diploe of the roof and to have grown upward mainly, to occupy most of the frontal fossa of that side. In case 8 the tumor arose subperi-orbitally to deform the upper portion of the orbit and did not give rise to the common dehiscence or fossa in the bone. In several cases the adjacent frontal sinus was encroached on, but in all cases these sinuses were

*Clinical Data on 9 Cases of Orbital Dermoid with Exophthalmos*

Case	Age, Yr.	Sex	Duration of Symptoms	Exophthalmos, Mm.	Roentgenographic Findings	Follow-Up Period; Outcome
1	11	M	1½ yr.	7	Circumscribed bean-shaped fossa in lateral wall of right orbit with diminished density	15 yr.; no recurrence
2	38	F	1 yr.	4	Circumscribed kidney-shaped hiatus in roof of left orbit with diminished density	1½ yr.; no recurrence
3	38	M	2 yr.	7	Well defined cystlike lesion in right frontal bone above zygomatic process	5 yr.; no recurrence
4	40	F	4 mo.	4	Deep fossa in frontal bone, extending up anteriorly from orbit with diminished density	3 yr.(?); no recurrence
5	63	M	5 yr. Recurrence 15 yr. after operation	11	Similar to findings in case 4	3 yr.; no recurrence
6	18	F	2 yr.	12	Massive cystic lesion with calcified walls occupying much of right frontal fossa and half of orbit	6 mo.; will recur, incomplete removal
7	47	M	6 yr.	20	Large mass of increased density occupying defect in left frontal bone, much of orbit and encroaching on frontal sinus with fossa in lateral wall of orbit	2 yr.; no recurrence
8	5	M	5 yr.	5	Enlargement of right orbit above, without typical appearance of dermoid	3 mo.
9	50	M	18 mo.	9	Oral hiatus in bone with sharp margin of increased density and diminished density of lesion itself	15 yr.; no recurrence

clear and the wall of the growth could be well distinguished. In the first and seventh cases the growth affected the lateral wall of the orbit or the greater wing of the sphenoid bone. In both cases it appeared as though the lesion arose from a subperi-orbital rest. In case 7 a tremendous tumor had arisen entirely within the orbit, associated with a small, nearly circular, dehiscence in the lateral wall beneath the sphenoid ridge. This opening in the bone should have indicated clearly the nature of the lesion in spite of the increased density of the shadow on the film, which was due to the high blood and/or hemosiderin content of the mass.

In differential diagnosis, several conditions must be considered. Retention cyst or mucocele of the frontal sinus may resemble a dermoid but may be distinguished by its connection with the sinus and the clouded condition of the sinus itself, together with absence of the characteristics of the dermoids previously given. A xanthoma of the bone or an eosinophilic granuloma may suggest a dermoid, but in such cases the criteria for dermoids are not satisfied, especially in respect to the increase in the density of the bone at the margins of the lesion. Invasion by a malignant tumor may have to be differentiated. Some resemblance was produced by a meningioma of the sphenoid ridge in a boy of 16, and this tumor, therefore, should be considered as capable of offering difficulty in differentiation. Meningocele may be confused with dermoid. The commonest site of this congenital opening in the bone is at the root of the nose, and it is indeed extremely rare (we have but 1 meningocele in our great collection of material). Saccular aneurysms of the internal carotid artery often erode the bone of the apex of the orbit and may also simulate a dermoid.

#### REPORT OF CASES

*CASE 1.—Dermoid (Oil Cyst), Subperiosteal of Right Orbit, Causing Exophthalmos. Fossa in Lateral Wall Revealed by Roentgenogram. Pre-operative Diagnosis of Dermoid. Operation, With Removal of Cyst. No Recurrence After Fifteen Years.*

H. B., a school boy aged 11, had had varying degrees of prominence of the right eye for the past one and a half years, without other symptoms. Vision was normal. There was no diplopia or muscular imbalance. Exophthalmos of the right eye measured 7 mm., with the eye displaced solidly forward. There was 1 mm. of papilledema in this eye.

Roentgenographic examination disclosed a sharply circumscribed, bean-shaped defect or fossa measuring approximately 15 by 30 mm. in the lateral wall of the right orbit between the superior orbital (sphenoid) fissure and the temporal line. The bone of the margins showed increased density, and the area within the confines of the margins revealed diminished density, suggesting an oil content. The bone of the floor of the indentation was extremely thin, but no dehiscence could be seen. All the paranasal sinuses were clear; the left orbit was normal; the optic canals were circular and symmetric and the calvaria was normal. The impression was that of a dermoid of the right orbit.

*Operation* (Dr. J. M. Wheeler).—Through an incision through the lateral canthus, a brownish mass was revealed in the lateral wall of the right orbit; the orbit was rather soft but had a firm ridge of elevated bone at its base. In an attempt to loosen the growth, the wall ruptured, and a large quantity of brown, greasy fluid with cholesterol crystals was liberated. The interior of the remaining sac was phenolized and washed with alcohol, after which as much as possible of the thin, friable wall was removed. The wound was closed with silk sutures, and a pressure dressing was applied. The course of recovery was uneventful.



*Pathologic Examination.*—The specimen consisted simply of a bit of lacrimal gland which had inadvertently been removed. The tissue showed infiltration with leukocytes, plasma cells and reticulum cells, with numerous capillaries.

*Subsequent Report.*—A follow-up examination fifteen years later disclosed no abnormality of the eyes.

*Comment.*—This case is a fine example of a dermoid, or oil cyst, of the orbit. The roentgenologic appearance was typical, and the treatment was definitive. It is probable that the exophthalmos had been present for several years before it was noticed by the parents. The inflammation revealed by the tissue of the lacrimal gland suggests the irritating nature of the cyst content.



Fig. 1 (case 1).—Subsuperior dermoid (oil cyst) of right orbit, producing a bean-shaped defect in the lateral wall, with characteristic roentgenographic findings.

*CASE 2.*—*Intradiploic Dermoid of Roof of Orbit, Involving Frontal Fossa and Producing Exophthalmos. Characteristic Defect of Bone as seen in Roentgenogram. Frontal Osteotomy and Removal of Growth.*

M. F., a white woman aged 36, had complained of periodic frontal headaches for many years; the attacks were brought on by dietary irregularities and were relieved by sleep. The left eye began to bulge eight months before her admission, and the exophthalmos had been increasing, without loss of vision and without double vision. This eye was observed to show 4 mm. of exophthalmos and to be displaced slightly inferiorly. Double vision could not be shown. Neurologic examination revealed nothing else of significance.

Roentgenographic examination disclosed a kidney-shaped defect in the roof of the left orbit, measuring approximately 1.5 by 3 cm. with sharp margins and a pronounced increase in the density of the surrounding bone. The area of the defect, or hiatus, showed striking diminution in tissue density. The left frontal sinus was small and uninvolved. All the paranasal sinuses were clear. The impression was that of a dermoid involving both the left orbit and the anterior cranial fossa.

*Operation (Dr. Charles A. Elsberg, of the Neurological Institute).—*Frontal flap was placed close above the left orbit, and a cystic cavity was opened as soon as the flap was raised. A great quantity of dark brown fluid was released from a large cystic cavity lying beneath the left frontal lobe, under and adherent to the dura and extending through a large defect in the roof of the orbit, to connect with a cystic recess within the orbit itself. The brownish fluid was full of cholesterol



Fig. 2 (case 2).—Intradiploic dermoid of the roof of the left orbit, producing a defect in the bone, through which the intracranial and the orbital portion of the growth communicated.

crystals. Several pieces of the cystic wall were removed, after which the cavity itself was thoroughly treated with Zenker's solution. Most of the cystic wall was excised, and at no time was the dura penetrated.

*Pathologic Examination.*—Specimens of the wall of the cyst consisted of heavy masses of hyalinized connective tissue, containing slits produced by the solution of cholesterol crystals. Squamous epithelium of a papillary type was evident and probably formed the lining membrane of the growth. No blood vessels or hair was in evidence. The diagnosis was epidermoid.

*Comment.*—This growth probably arose from a diploic epidermal rest and, because of the absence of blood vessels, hair, and other dermal structures and because of the concentrated content, should be regarded

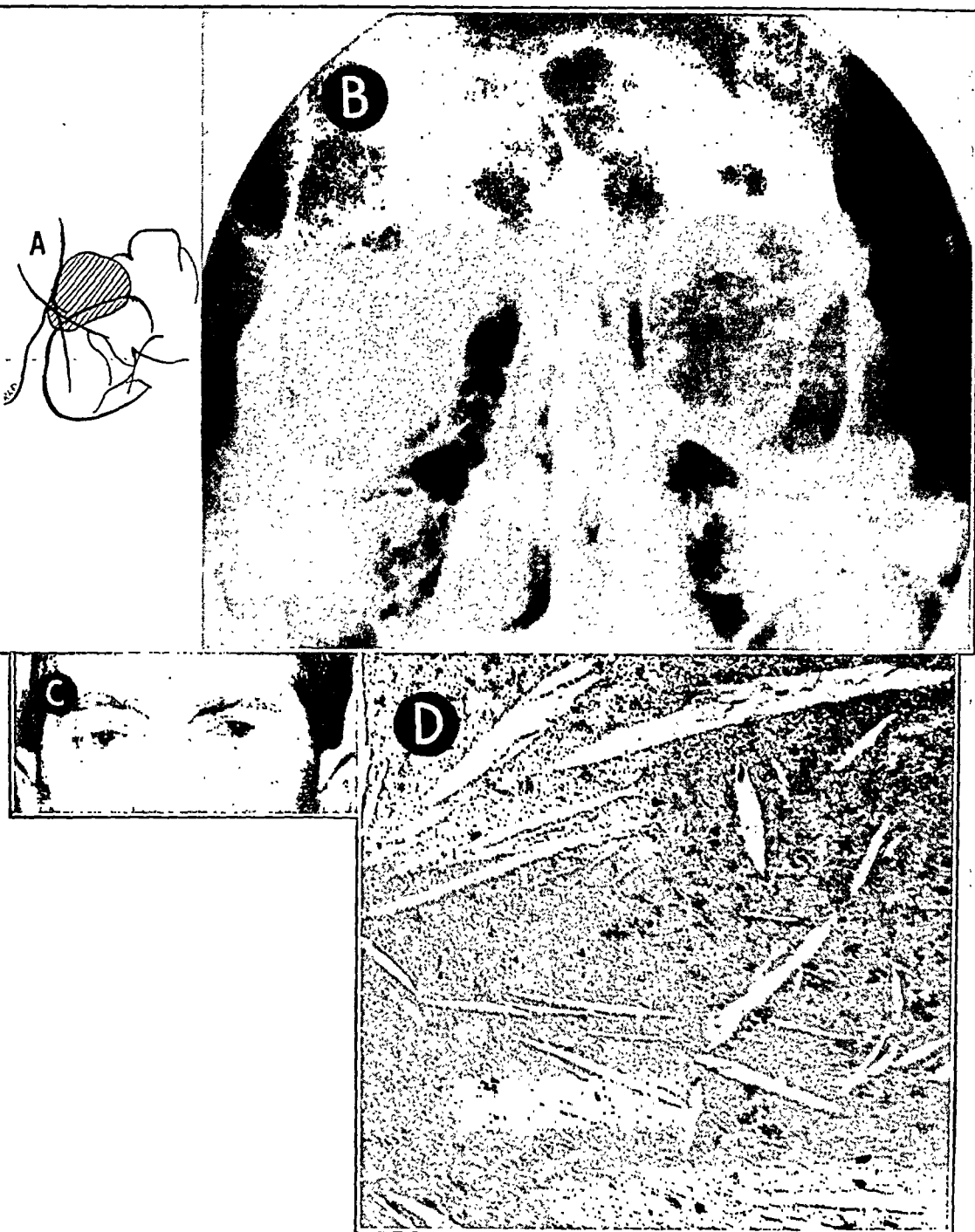


Fig. 3 (case 3).—Intradiploic dermoid of frontal bone, revealing roentgenographic characteristics of circumscribed margin with increased density of bone at the margin and diminished density of the growth itself. Note calcium in wall of the cyst bulging into orbit. *D* shows cholesterol crystals in amorphous contents of the cyst. See description in text.

as an epidermoid. The tumor was of especial interest because of the dumb-bell shape, with one portion in the orbit and the other within the cranium and external to the dura mater.

*CASE 3.—Dermoid, Intradiploic, in Roof of Right Orbit, Causing Exophthalmos. Cystic Defect Revealed Roentgenologically. Preoperative Diagnosis: Dermoid. Operation and Removal of Cyst.*

D. R., a white man aged 38, a plumber by trade, had had increasing exophthalmos of the right eye for two years. There were no other symptoms or complaints. Vision was normal, with correction, and there were no field defects or changes in the fundus. The right eye was displaced solidly outward and downward, with exophthalmos measuring 7 mm. There was left hypertropia, which increased with the eyes looking up and to the right.

Roentgenographic examination revealed a cystlike defect, measuring 2.5 by 3 mm., in the roof of the right orbit above the zygomatic process and fossa for the lacrimal sac, with sharply circumscribed margins and some increase in the density of the bone at the margins. The lower extent of the lesion was revealed in the orbit by calcium in the capsule or wall. The area within the margins showed diminished density of the tissue, suggesting oil or fat. This cystic lesion



Fig. 4 (case 4).—Diploic dermoid of frontal bone of left side deforming orbit and producing severe exophthalmos.

did not connect with the right frontal sinus, which lay adjacent and which appeared indefinitely clear. The impression was that of dermoid cyst of the roof of the right orbit.

*Operation* (Dr. R. L. Pfeiffer).—Through an incision made over the outer half of the superior margin of the orbit down to the bone, the periorbita was elevated and dissected back to expose a firm, bulbous, brown mass. This mass was opened to liberate a large quantity of oily fluid with semisolid, yellowish material, which glistened. The sac was cleaned out thoroughly and treated with phenol and alcohol, after which the lower wall was removed with as much of the lining as could be stripped away. The wound was closed tightly and a pressure dressing applied. Healing was uninterrupted.

*Microscopic Examination.*—The specimen consisted of a fragment of the cyst wall. This was composed of connective tissue in which there were many spaces occupied by cholesterol crystals, some bone formation, old hematogenous pigment and some lymphocytic infiltration. There were a number of foreign body giant cells, which appeared mostly in relation to the sites of the cholesterol crystals. There were only faint suggestions of epithelial remnants, and no gland structures or hair follicles were noted. The diagnosis was degenerative changes incident to a dermoid cyst.

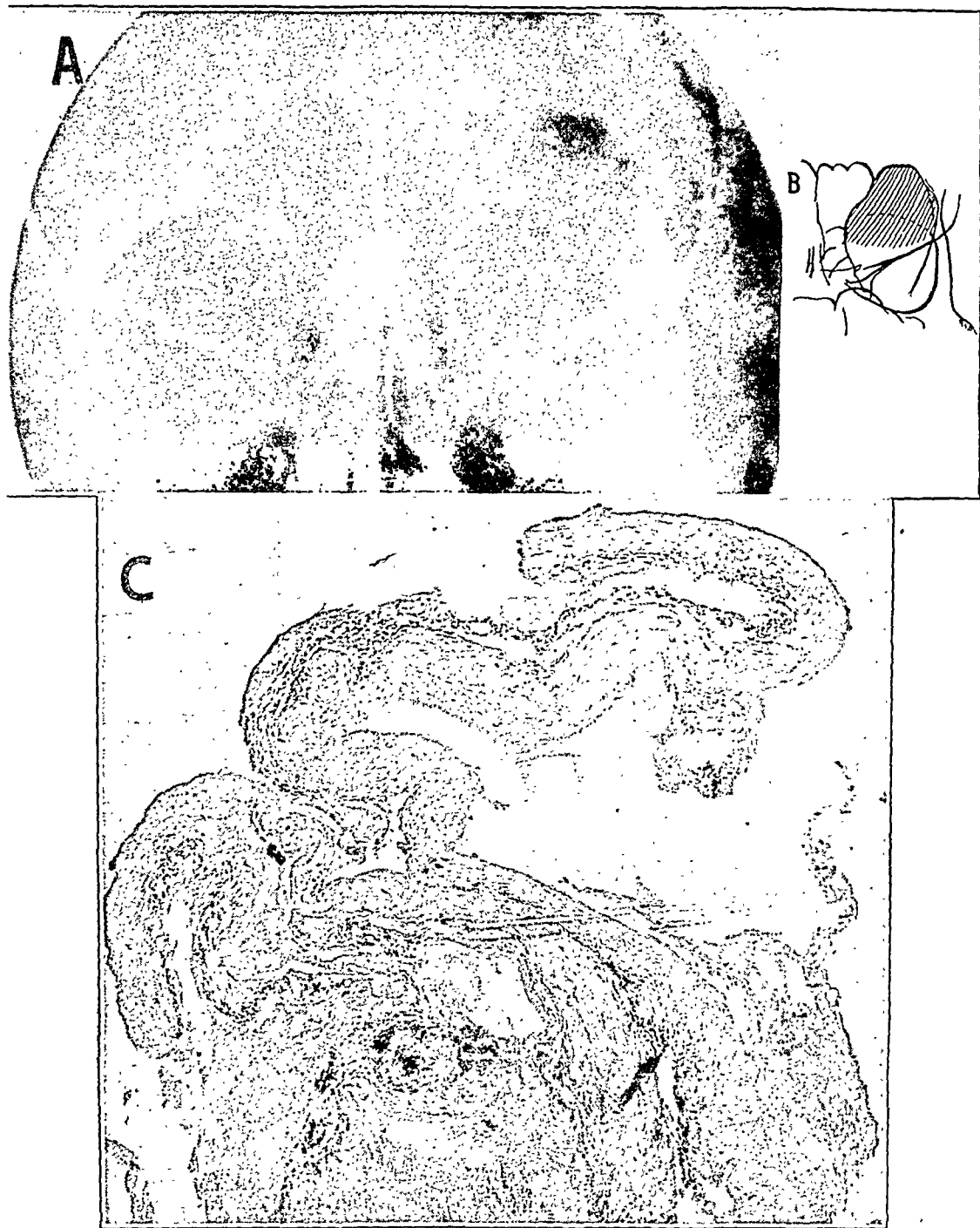


Fig. 5 (case 4).—Diploic dermoid of left frontal area. The inferior limit of the cyst is not visible roentgenographically. *C* shows portion of wall of cyst under low power magnification.

*Comment.*—There was no evidence of recurrence after an interval of five years.

*CASE 4.*—*Dermoid, Diploic of Left Orbit, Causing Exophthalmos. Large Defect or Fossa in Roof of Orbit Shown in Roentgenogram. Preoperative Diagnosis: Dermoid. Operation, With Removal of Cyst.*

D. P. A., a married white woman aged 40, had had partial ptosis of the left upper eyelid since a sinus infection eight years earlier. The eyeball began to protrude four months prior to admission, and exophthalmos measured 4 mm. There was no discomfort or diplopia. Vision was normal with correction. The fundi were normal. A mass was palpable above, displacing the eye downward and outward.

Roentgenographic examination revealed a large excavation or fossa in the roof of the left orbit with sharp margins, slight increase in bone density at the margins and diminished density of the lesion itself. This fossa measured approximately 2 by 3 cm. and lay adjacent to the frontal sinus, on which it encroached but with which it did not connect, since a well defined wall of the cystic cavity could be distinguished at this point. No definite inferior margin



Fig. 6 (case 5).—Patient with dermoid of the frontal bone. He had been treated repeatedly by aspiration with inflammation of orbit resulting from leakage into the orbit of the toxic content of the cyst. This cyst had recurred twenty years after supposed complete extirpation.

of the lesion was evident. The orbit showed increased density of soft tissues and increased intraorbital pressure. The impression was that of dermoid cyst, diploic in origin.

*Operation* (Dr. M. Wheeler).—An incision at the orbital margin above revealed a brownish mass bulging into the orbit; the growth was approximately the size of a golf ball, firm to the touch and fixed in position. An incision released a great quantity of brownish yellow, oily fluid with large masses of glistening material, which obviously was cholesterol. The cyst was cleaned of its content, treated with phenol and alcohol, and as much of the wall as possible was dissected away. The course of healing was uneventful.

*Pathologic Report.*—Examination revealed an epithelium-lined cyst with cholesterol clefts, fibrous outer wall, hemosiderin, chronic inflammation and products of degeneration. The diagnosis was dermoid cyst involving the orbit.

*Comment.*—This case would seem to represent a later stage of the same type of lesion, and in a similar position, as that in case 3. In

case 5 the cyst in the roof of the orbit appears to be in an even later stage, also to arise in a similar position. The deep defects in the bone attest the congenital origin of these lesions.

*CASE 5.—Dermoid Cyst, Diploic, of Roof of Orbit, Causing Extreme Degree of Exophthalmos. Huge Defect or Fossa in Roof of Orbit Revealed in Roentgenogram. Recurrence. Preoperative Diagnosis: Dermoid of Orbit. Operation, With Removal of Cyst.*

M. P., aged 63, a white cabinet maker, had had exophthalmos of the left eye, with operation and removal of a cyst from the orbit twenty years before in Germany. Fifteen years later the eye began to bulge again. A large, fluctuant mass could be palpated above, displacing the eye down and outward 11 mm. Both lids were edematous. The patient refused to be hospitalized, and the referring physician requested that the cyst be drained by trocar. A large quantity (18 cc.) of chocolate-colored, oily fluid with small masses of cholesterol was withdrawn and the eye returned to a more normal position. One month later, the patient returned with the eye as prominent as before. Again the cyst was drained, but a considerable reaction followed. The eyelids were tremendously swollen, tender and sore. Several weeks later hospitalization was effected, and the cyst was removed.

The roentgenographic report described a very large cavity in the roof of the orbit, measuring 3 by 5 cm., posterior to the margin with clearcut edges, some increase in bone density in places at the margin and diminished density of the lesion itself. A definite cyst wall could be distinguished bulging into the orbit. The zygomatic process of the frontal bone was thin, atrophic and deformed. The dimensions of the orbit were increased, evidencing a lesion of long duration. There was no communication with the adjacent, normal, frontal sinus.

*Operation* (Dr. R. L. Pfeiffer).—Through an incision below the brow, a chocolate-colored mass was exposed under a greatly thinned orbital margin, which was removed in part. The fluctuant mass was incised, and the brownish yellow, oily fluid was liberated, with large, cakey, yellowish, glistening masses of cholesterol. No hair was seen. The cavity, large enough to accommodate a golf ball, was cleaned, treated with phenol and alcohol and then dissected out as completely as possible. The wound was closed without drainage, and healing was uneventful.

*Pathologic Report.*—Examination revealed a fibrous, inflammatory mass with foreign body giant cells, cholesterol crystals and hemosiderin. Epithelium was not found. The diagnosis was cholesteatoma.

*Comment.*—The severe inflammation which followed the second drainage was probably due to the toxic content of the cyst coming in contact with surrounding tissues at the orbit. Obviously the dermoid cyst cannot be drained successfully. It must be removed carefully and completely.

*CASE 6.—Dermoid, Diploic, Occupying Right Anterior Cranial Fossa, Encroaching on Orbit, to Cause Exophthalmos. Calcified Area in Wall of Growth, Size of Tennis Ball, Revealed in Roentgenogram. Preoperative Diagnosis: Dermoid. Operation, With Partial Removal of Tumor.*

C. M., an 18 year old Negro girl from Jamaica, in good health, complained of increasing prominence of the right eye for the past two years. The eyeball was

displaced down and outward, with exophthalmos measuring 12 mm. A firm mass could be felt above through the upper lid, and prolapse of the lacrimal gland was apparent. Vision in each eye was 20/15 with correction. Diplopia was not bothersome.



Fig. 7 (case 5).—Large diploic dermoid of the frontal bone deforming the orbit and producing very severe exophthalmos. Note calcium in inferior wall of cyst. C (high power section) shows tissue described in text.

Roentgenographic examination disclosed a cystlike, spherical mass the size of a tennis ball in the right frontal fossa and encroaching on the orbit. The wall of the cyst was densely calcified and was complete above and thin below in the orbit, where a thin, linear shadow of calcium extending midway down



into the orbit located its inferior limitation. The roof of the orbit had been completely replaced from the margin in front to the sphenoid ridge posteriorly. The content of the mass showed diminished density. The diagnosis was dermoid cyst of extraordinary proportions arising in the roof of the right orbit or in the frontal fossa and encroaching on the orbit, to produce exophthalmos.

*Operation* (Dr. J. Scarff of the Neurological Institute).—Through an osteotomy opening in the right frontal area, a large cystic cavity was entered and observed to be filled with a thick, mucilaginous, brownish fluid containing hemosiderin and

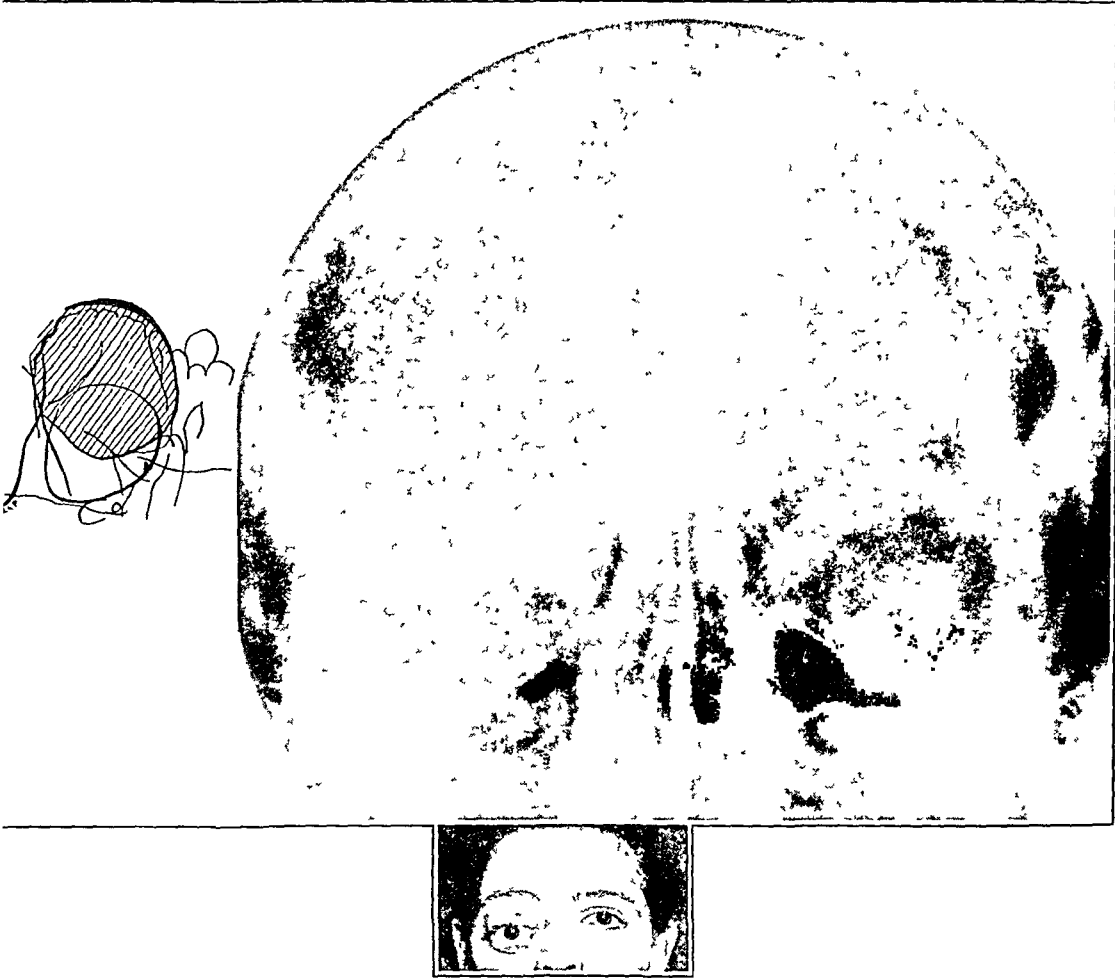


Fig. 8 (case 6).—Diploic dermoid arising in bone of roof of right orbit, reaching startling size, to occupy much of the right frontal fossa and orbit and producing extreme exophthalmos. Calcium can be seen in all parts of the wall of the cyst.

cholesterol. The cyst was drained of content and was found to be multiloculated and lined with stratified squamous epithelium. A mass of solid tissue was found in a recess and was removed. The inferior wall of the cyst in the orbit was excised in part to decompress the orbit and allow the eye to assume a better position.

*Pathologic Report.*—The specimen consisted of bone invaded by a cystic epithelial tumor. In the hollowed bone a poorly demarcated band of layered

epithelium rested on a thin layer of loose-meshed connective tissue. The epithelial cells in areas were observed to be undergoing degeneration, with clusters of hemosiderin-laden phagocytes among them. Masses of cholesterol were evident.

*Comment.*—This tremendous cyst, which occupied most of the right frontal fossa and half the right orbit, produced extreme exophthalmos but no profound symptoms. There were no symptoms relating to the central nervous system, and vision in the right eye was normal. The cyst seemed to have arisen in the diploic bone of the roof of the orbit as a congenital epithelial rest to grow in all directions—expanding as a spherical mass to reach startling dimensions.

The excision of the cyst was incomplete, and subsequently several aspirations of as much as 20 cc. of chocolate-colored fluid were performed six weeks after the operation. The area of the excised bone of the right frontal region was distended when last examined, and the position of the eye was unimproved.

*CASE 7.—Dermoid of Left Orbit, Apparently Subperiosteal, Causing Exophthalmos. Mass in Enlarged Orbit Revealed in Roentgenogram. Preoperative Diagnosis: Pseudotumor or Dermoid. Operation: Removal of Large Dermoid.*

R. H., a white man aged 47, gave a history of having had a sinus operation eight years before, without benefit. Six years later the left upper eyelid began to droop, and subsequently the eyeball was displaced from the socket to such a degree that it was impossible for him any longer to close his eye, except with the use of his hand. Double vision developed, but subsequently the vision of the eye failed and he was no longer bothered. No pain or distress was noted. Examination disclosed the right eye to be normal and the left to be displaced outward and downward, with approximately 20 mm. of exophthalmos. A large and very firm mass could be palpated through the upper lid. Vision in the eye was 20/100, and slight papilledema was manifest. There was limitation of motility in all directions, most marked superiorly.

Roentgenographic examination disclosed that the right orbit was normal and the left greatly enlarged in all dimensions, with a mass of increased density above, the tumor thinning and elevating the roof of the orbit anteriorly, where a dihcence in the bone was apparent. Medially, the mass bulged into the frontal sinus, which cell was otherwise perfectly clear. An oval defect or opening, measuring approximately 0.5 by 2 cm., was present in the lateral wall of the orbit posterior to the temporal line. The margins of the defect were clearcut, and in places increase in the density of the bone could be seen. The density of the tissue in the defect was diminished, in contrast with most of the tissue above. The zygomatic process of the frontal bone was thin and atrophic where the mass impinged on it. The nasal wall of the orbit was concave, and the floor was depressed slightly into the antrum. The optic canals were circular, measured 5.5 mm. in diameter and were symmetric.

*Impression.*—A large mass, measuring approximately 4.5 by 4 cm., with increased tissue density for the most part, was present in the left orbit, extending upward to produce pressure atrophy and displace the roof anteriorly. An oval defect with diminished density was present in the lateral wall. That the adjacent frontal sinus was clear made it improbable that the lesion arose within it and thus excluded the possibility of mucocoele. The defect in the lateral wall was more consistent with the diagnosis of pseudotumor but was suggestive of a congenital lesion, probably a dermoid.

*Operation* (Dr. R. L. Pfeiffer).—A curvilinear incision was made over the margin of the orbit above down to the periosteum, which was raised to expose a chocolate-colored mass beneath. The margin of the orbit was sharp and thin as a result of pressure. An incision was made into the tumor, and a great quantity of semifluid, dark brown matter resembling thick mud, though with cholesterol crystals evident, was spooned out. The wall of the tumor was firmly adherent above, and a large, smooth, soft and fluctuant area was palpated in the roof of the orbit. This represented the dehiscence seen roentgenographically and was no doubt the dura presenting in it. At several places within the wall of the cyst bleeding developed but was not troublesome. The lining of the cavity was treated with phenol and alcohol and was washed with saline solution. Subsequently, as

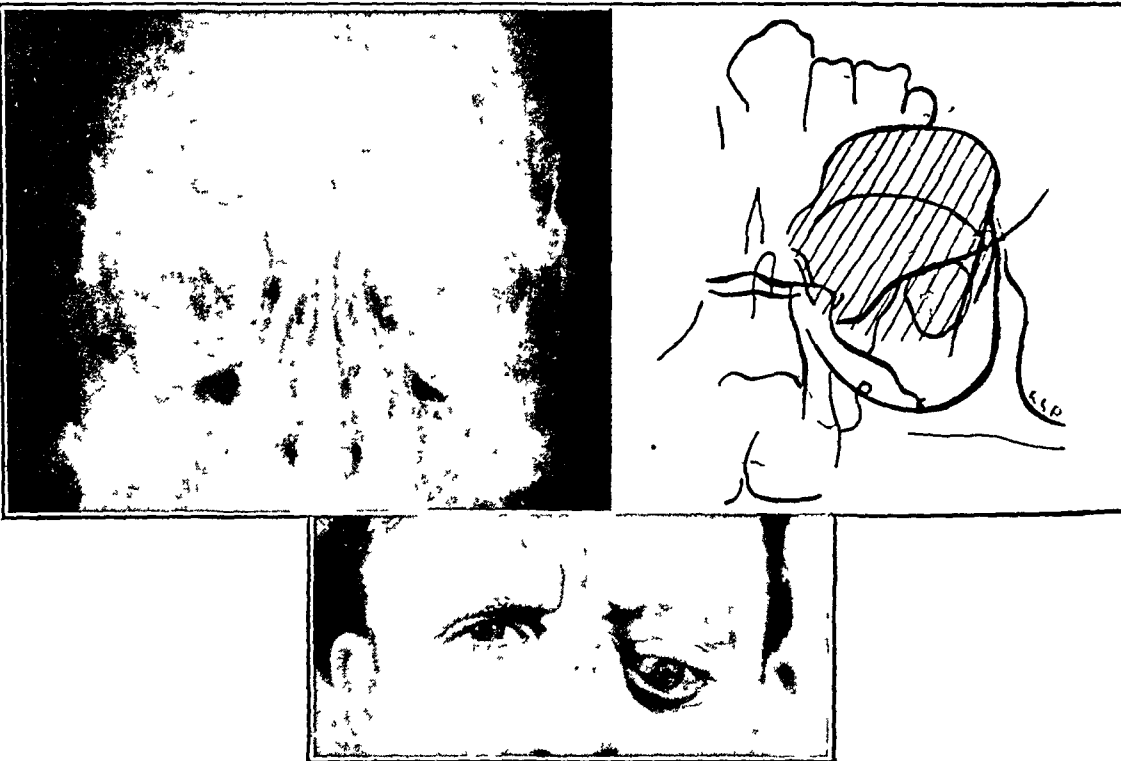


Fig. 9 (case 7).—Subperiosteal dermoid of left orbit with unusual features. The increased soft tissue density of the mass itself is due to the great hemosiderin content. A fossa of diminished density can be seen in the lateral wall, with typical appearance.

much of the wall was removed as was feasible. At operation considerable care should be exercised that the roof of the orbit not be perforated.

*Pathologic Report.*—In a specimen consisting almost completely of an encapsulated mass of tissue, the bulk of which consisted of spaces containing cholesterol and surrounded by a foreign body cell reaction, many large foreign body giant cells, some containing blood pigment, were observed. The cholesterol spaces were lined with rather flat cells, which did not look like epithelium. Large foam cells, suggesting fat necrosis, were present. Considerable blood pigment, especially in the connective tissue capsule, suggested possible pressure necrosis of fat by hemorrhage. The diagnosis was cholesteatoma.

*Follow-up Period.*—After the operation the eye returned to a much improved position, with exophthalmos of 2 mm. remaining and displacement of the eye inferiorly 2 or 3 mm. Partial ptosis persisted. Vision in the eye was 20/40 with correction and the fundus was normal. Through a two year follow-up period no change was observed. The patient died subsequently of a heart attack.

*Comment.*—The roentgenographic findings in this case were confusing. The increased soft tissue density of the main portion of the mass was probably due to the large amount of hemosiderin. Hemorrhage had probably taken place repeatedly within the growth. The

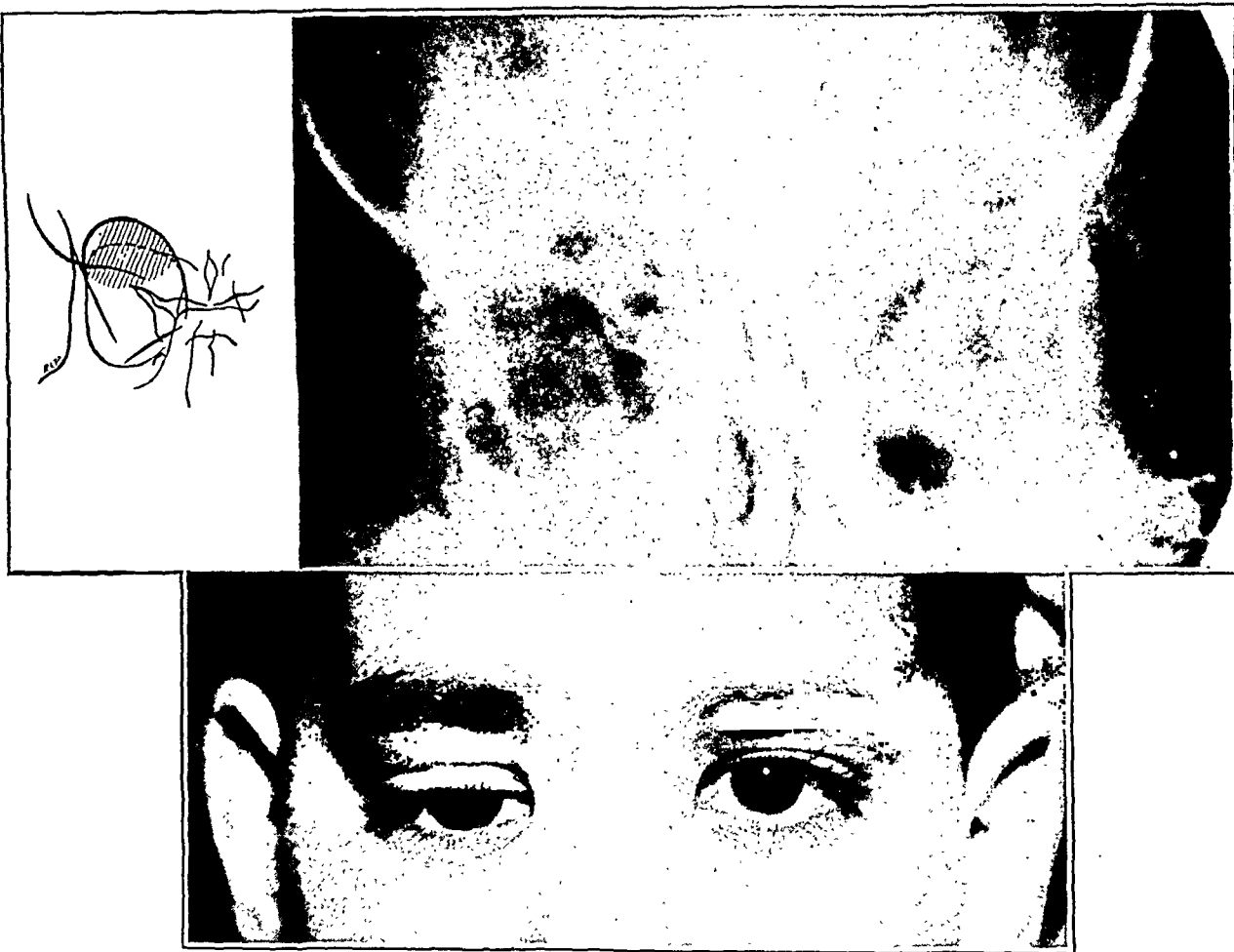


Fig. 10 (case 8).—Dermoid of right orbit perhaps subperiosteal, producing unusual deformity. This is the only growth in which hair was found.

great masses of cholesterol, the fibrous capsule with blood vessels, the absence of communication with the paranasal sinus and the presence of a characteristic defect in the lateral wall of the orbit, all serve to make this an undoubted case of dermoid, probably subperiosteal or diploic in origin.

*CASE 8.—Dermoid of Right Orbit, Producing Exophthalmos and Ptosis. Deformity of Orbit Revealed in Roentgenogram. Preoperative Diagnosis: Hemangioma. Operation, With Removal of Dermoid.*

D. E., a white boy aged 5 years, had been observed to have an abnormality of the right eye since birth, marked chiefly by drooping of the eyelid. Prominence of

the right eye had been observed recently. There were no other symptoms or signs. Examination disclosed the right eye to be displaced forward and inferiorly, the exophthalmos measuring 5 mm. Partial ptosis was manifest. Vision of each eye was normal with correction. Except for the weakness of elevation of the eyelids, the extraocular muscles appeared uninvolved. A firm mass could be palpated above the globe and was found to be thoroughly fixed in position. The visual acuity and fundi were normal.

Roentgenographic examination revealed marked asymmetry in the orbits. The left was normal, and the right showed increased capacity with only the vertical dimension increased. The left orbit measured 33 by 40 mm. while the right

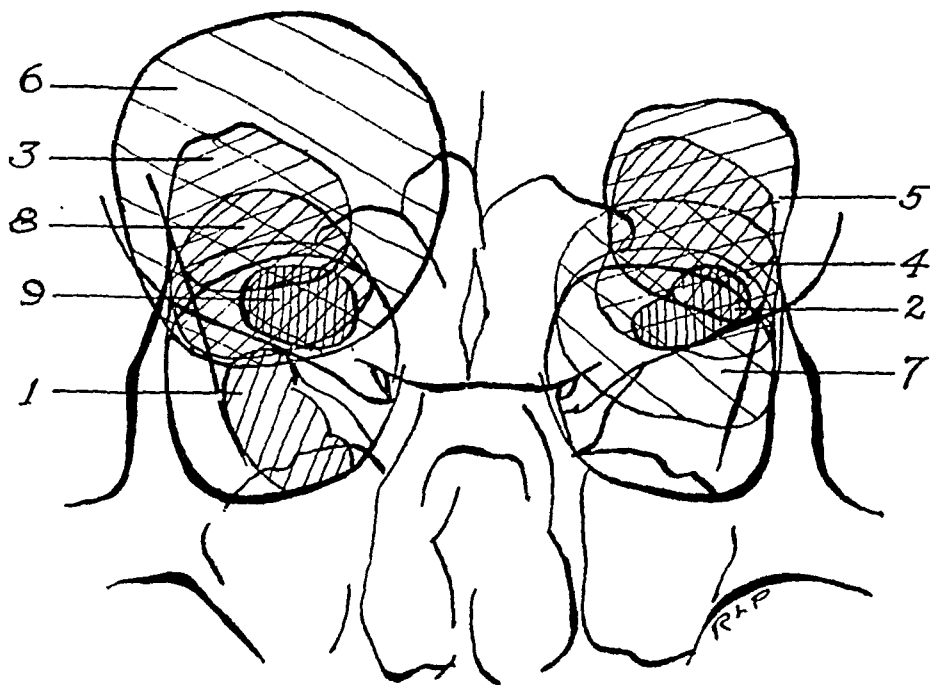


Fig. 11.—Line drawing indicating the locations of the 9 dermoids and their relative sizes.

measured 33 by 50 mm. Thus the deformity of the right orbit was in the upper portion and the roof. The bone of the roof of the orbit was intact throughout, and increased density of the soft tissue was manifest. The sphenoid ridges, sphenoid fissures, temporal lines and optic canals were symmetric. The right antrum was clouded.

*Impression.*—The extraordinary deformity of the right orbit was undoubtedly congenital and was most suggestive of an hemangioma.

*Operation* (Dr. J. H. Dunnington).—An incision was made along the upper margin of the right orbit down to the periosteum, which was raised from the bone. The dissection was carried posteriorly over the margin, and a brownish mass was encountered. The exposure was improved, and an incision was made in the tumor. A great deal of cheesy material with hair was liberated. The tumor sac was subsequently dissected out and removed *in toto*. The periosteum

was closed with surgical gut sutures and the cutaneous incision with silk. An intermarginal suture was used to close the eye, after which a pressure dressing was applied.

*Pathologic Report.*—The specimen was a cyst, the wall of which was missing at one point. The cystic space was lined with keratinized epithelium. In the fibrous wall around this epithelium were rudimentary glands. No hair follicles

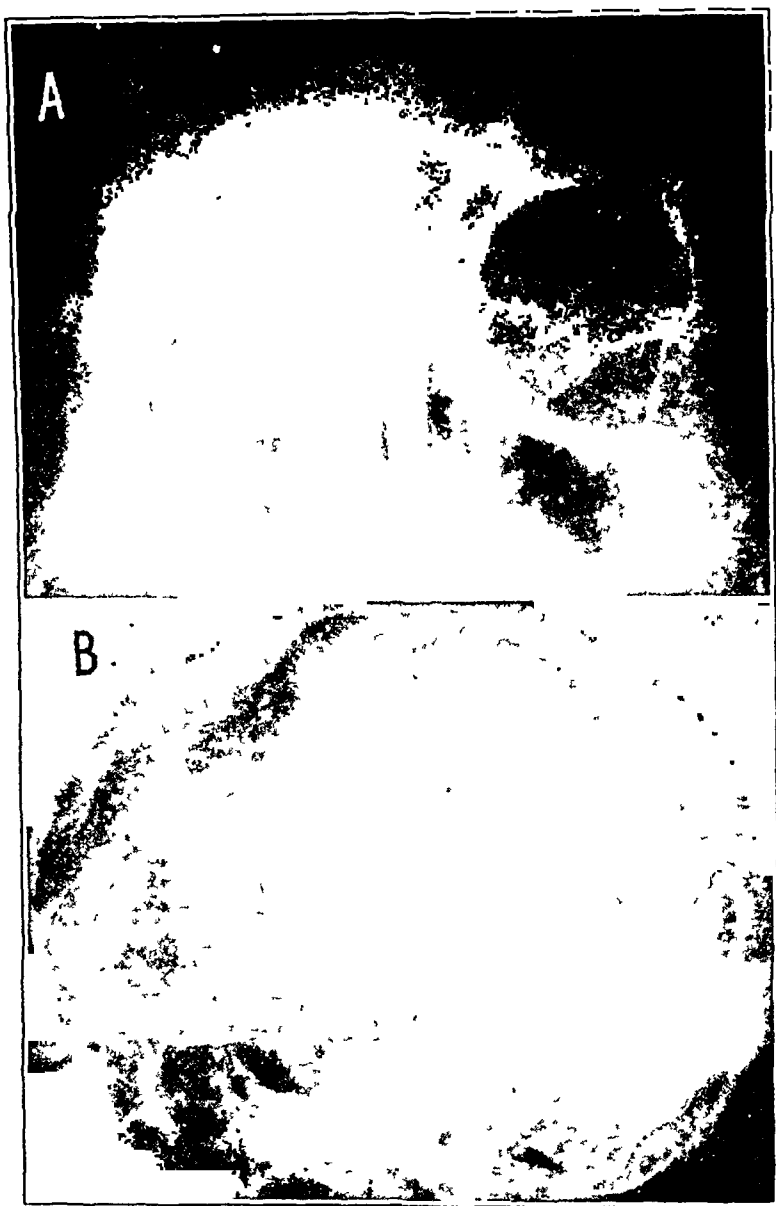


Fig. 12.—*A*, roentgenogram showing dermoid involving the left orbit; *B*, roentgenogram showing a typical dermoid of the vault of the skull.

were seen. There was also rather diffuse lymphocytic infiltration, which in places formed focal accumulations. The diagnosis was dermoid cyst.

*Comment.*—Hair was found in the cyst at operation but was not reported to be present in the specimen examined in the laboratory. The deformity of the orbit in this case was not typical of dermoid. Its congenital character, however, was apparent.

CASE 9.—*Dermoid, Diploic, of Right Orbit, Causing Exophthalmos. Hiatus in Roof of Orbit Evident in Roentgenogram. Operation, With Removal of Dermoid Cyst.*

S. S., aged 50, a white man with moderately severe diabetes, had observed poor vision in his right eye three years previously. Eighteen months prior to

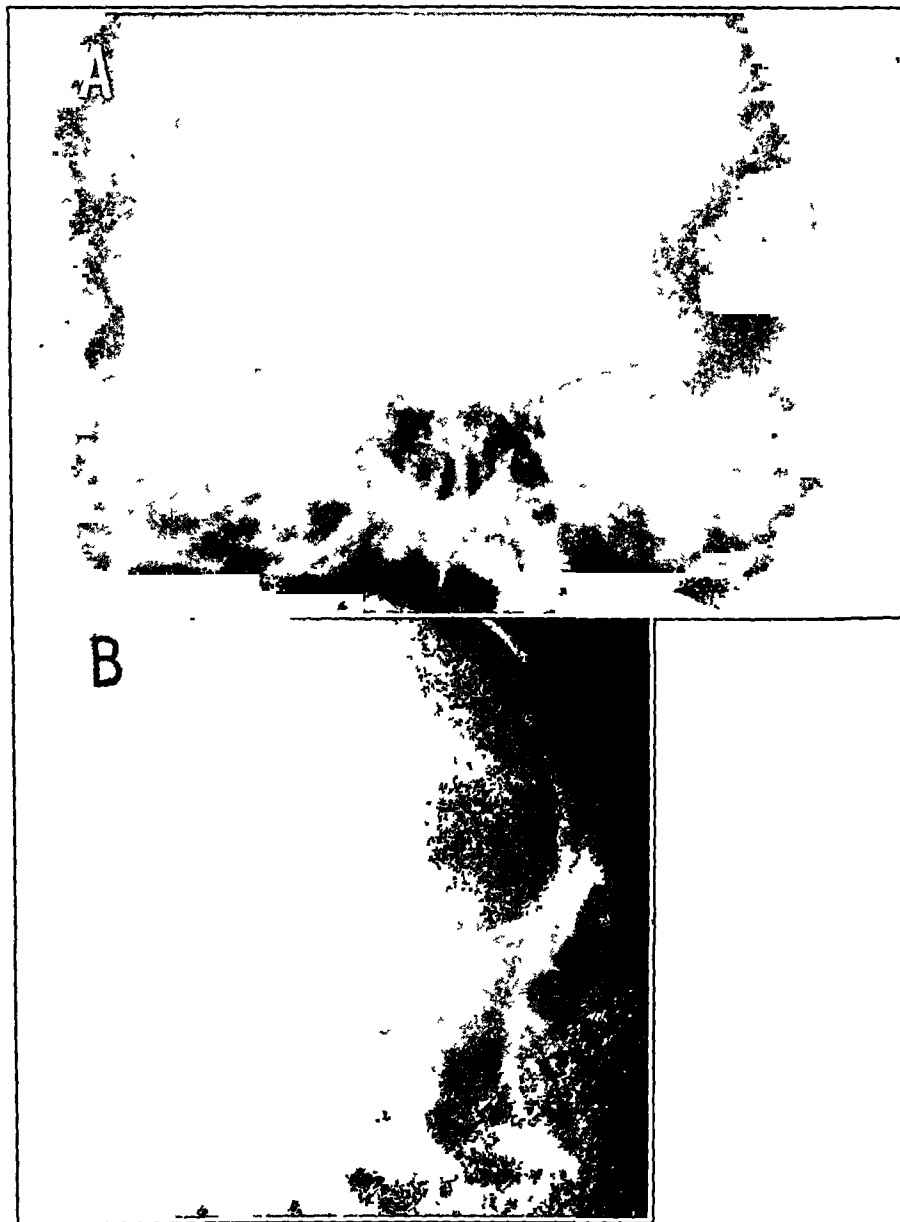


Fig. 13.—Roentgenograms of a dermoid of the left orbit (same patient).

examination double vision developed, and at the same time the eyelids began to droop. Subsequent to this the right eye became prominent, and the prominence had increased. The left eye was normal. Examination disclosed vision of 20/200 in the right eye and 20/30 in the left eye, the latter being entirely normal. The right eye was displaced forward and downward, and exophthalmos measured

9 mm. There was limitation of motility, most pronounced in the field of action of the internal rectus muscle. A mass could be felt above the eye. Ptosis was complete, and the lid could be raised voluntarily. Except for elevation of the blood sugar, the blood chemistry was normal and tests revealed nothing significant.

Roentgenographic examination of the orbits revealed an oval, sharply circumscribed defect, or opening, approximately 2 by 3 cm., in the roof of the right orbit. All the adjacent sinuses were clear, and the sella turcica was normal.

*Operation* (Dr. John H. Dunnington).—Through an incision in the upper lid of the outer margin of the orbit a large, dark brown, firm mass was revealed attached to the roof of the orbit. The mass was incised, and a large quantity of dark brown, oily fluid with shining crystals and soft masses of mudlike material was evacuated. An opening, measuring 20 by 30 mm., was observed in the roof of the orbit, through which the dura was pulsating. This opening appeared to lie in the middle third of the orbit anteriorly. As much as possible of the wall of the cyst was excised.

*Microscopic Examination*.—Fragments of tissue removed for study revealed that the cyst wall consisted of dense fibrous tissue with much hemosiderin and clefts containing cholesterol. Spaces lined with epithelium were observed, and in places degenerated fat or foam cells were evident. In other areas the tissue appeared rather necrotic, loose and fibrous, with hemosiderin pigment, and in places areas of fresh blood were seen. Throughout this tissue were abundant cholesterol crystals, surrounded by multinucleated foreign body giant cells. No hair was observed. The diagnosis was cholesteatoma of the orbit, probably of diploic origin.

*Comment*.—This patient was followed in the clinic for fifteen years, without any evidence of recurrence of the cyst, although not all the cyst wall had been excised and phenolization was not employed.

#### TREATMENT

Since dermoids of the orbit vary in size, position and composition and may involve neighboring structures and cavities, their treatment requires thorough study of the case and careful planning.<sup>26</sup> Deformity of the orbit is the rule, and proper roentgenographic examination is essential for diagnosis; in addition, the plan of treatment rests on the defect revealed. If a hiatus is found in the roof of the orbit, the frontal fossa may be involved, and thus the service of a neurosurgeon may be needed, as in cases 2 and 6. In all cases it rests with the roentgenologist to decide whether or not the defect extends through the bone and possibly involves the adjacent cavity.

In 6 of the 9 cases, direct approach through incision at the margin of the orbit over the presenting masses was adequate. In these cases the periorbita was raised and the bone was followed back to the lesion, which was incised and evacuated. The remaining sac was then phenolized, next treated with alcohol and then irrigated with saline solution. The cyst wall was then removed as completely as possible. The wound

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26. Gifford, H.: Treatment of Dermoid Cysts of Orbit, Arch. Ophth. 52:448 (Sept.) 1923; Recurrent Dermoids, *ibid.* 2:305 (Sept.) 1929.



was finally closed tightly in layers, and a pressure dressing was applied, to remain for several days.

Obviously, temporization is not justified. Because of the toxic character of the content of the cyst, aspiration not only will fail to improve matters but also may produce intractable inflammation in the orbit.

#### SUMMARY AND CONCLUSION

In this paper we suggest the incidence of dermoids and epidermoids, differentiate the one from the other and endeavor to clarify the terminology. Because there is little embryologic and histologic distinction between these growths, it is contended that the name "dermoid" is sufficient to cover both. Intermediate or transitional types are common, and the assumption of a purely arbitrary condition, such as the presence or absence of hair, to differentiate them is not applicable or practical.

All the 9 dermoids involving the orbit and causing exophthalmos reported here were cystic, with epithelial linings which varied greatly in number of layers and appearance of cells and with the content of the cavities consisting of fluid and semisolid matter. The fluid was oily, brown or chocolate in color, due to hemosiderin, and served as a solvent for cholesterol. The semisolid matter consisted of cholesterol and epithelial products. Hair was found in only 1 case.

This series of cases is presented primarily to call attention to defects in the bone which they produce, which may be well studied by roentgenography, and which serve to distinguish these lesions from other causes of proptosis. The characteristic roentgenographic appearance of such a lesion of the bone is that of an area of diminished density with smooth, regular margins of increased density of the bone.

Caution on treatment, whether by neurosurgeon or ophthalmic surgeon, which is determined by roentgenography, is duly stressed. The proper use of phenolization is mentioned.

## A SIMPLE OPERATION FOR ENTROPION

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IT IS the purpose of this report to review the mechanism of so-called spastic entropion of the lower lid and to call attention to a simple and effective operation for this condition. This procedure is directed toward correction of the abnormal anatomic relations which predispose to malfunction of the orbicularis oculi muscle.

Many operations have been described for the correction of spastic entropion, but none is directed at correction of what seems to be the fundamental cause, namely, an abnormal relation of the tarsal plate to the globe, with resultant improper function of the orbicularis oculi. In some previously described procedures attempts have been made to modify the action of the orbicularis on the tarsus or to buckle the tarsal plate outward either by establishing an everting cicatrix or removing a wedge from the outer surface of the plate parallel to the lid. Other procedures have been directed toward tacking the lower border of the tarsus to the periosteum of the bones of the face either by sutures or by transplanting a strip of orbicularis. Even resections of the skin have been advocated to prevent the lower tarsal margin from everting by tightening the skin of the lids. Only Graefe seems to have considered removal of a wedge from the inferior margin of the tarsus to change its curvature, and then only as a supplemental procedure to his operation for cicatricial entropion.

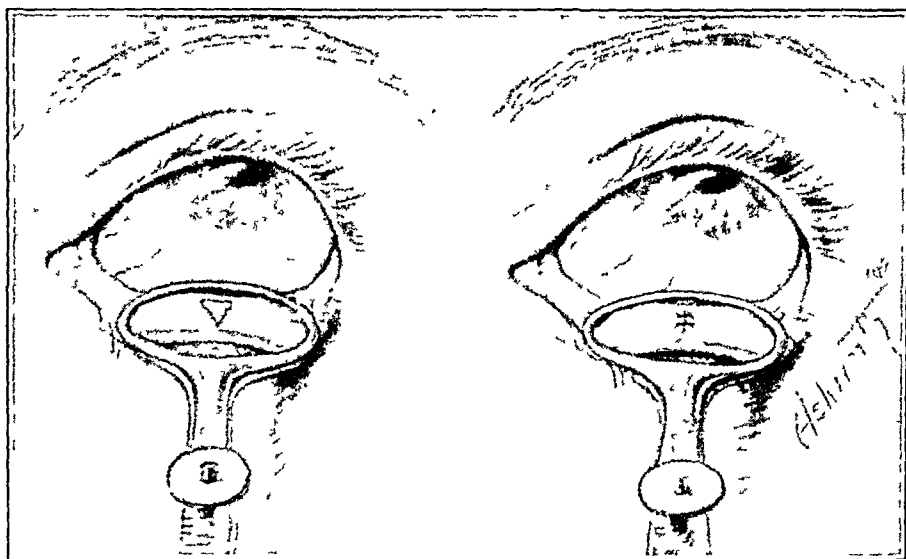
The tarsal plate is the "skeleton" of the lid and is of the utmost importance not only in maintaining its shape and function but also in directing the action of the orbicularis muscle. In effect, the tarsus is a curved flap of relatively nonelastic connective tissue suspended by tarsal ligaments at its upper outer margin. The lower border is attached to the orbital septum and to an expansion of the fascial sheath of the inferior rectus muscle. In this lies the inferior palpebral (involuntary) muscle. These attachments are relatively loose.

Normally the tarsal plate has a double posterior concavity, which allows it to conform to the shape of the globe. This rather marked anteroposterior concavity of the plate is maintained even in closure of the lids because the lateral palpebral ligaments are attached within

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From the Department of Ophthalmology, University of Oregon Medical School.

the orbit well behind the limbus and the tarsus is molded on the eyeball. In normal lid closure the orbicularis elevates the lid margin, stretches the skin smoothly over the lower lid and applies direct pressure to the tarsal plate, thus maintaining its normal snug relation to the globe. In this case the tarsus slides smoothly over its bed, without abnormal rotations occurring. If, however, there has been absorption of orbital and suborbicularis fat, with relaxation of the inferior ligaments, the normal relations of the muscle, tarsus and globe are no longer maintained. Contraction of the orbicularis now straightens the lid margin and tends to force it down, thus relaxing the inferior ligaments. A straight axis is now provided by the shortened and straightened upper border around which the tarsus may rotate in a flaplike manner. In entropion the lack of support by the globe and the relaxation of the inferior ligaments allow



Area of tarsectomy and line of closure.

the lower border of the tarsus to rotate outward around this axis, with the resulting inversion of the upper border. The rubbing of the cilia against the globe stimulates blepharospasm, which tends to exaggerate the condition.

In spastic entropion the normal curvature of the tarsal plate is lost and the inferior border no longer fits the globe snugly, owing to varied changes in elasticity of the tissues and absorption of suborbicularis and orbital fat. In effect, the lower tarsus has become relatively too long and too flat. To correct this and to restore the normal snug relationship of the tarsus to the globe, an inverted wedge is excised from its inferior margin of the tarsus to shorten and, thereby, to increase the curvature of the lower part without disturbing the ligamentous attachments or the orbicularis muscle.

The operation can be performed in a minor surgery room with the use of local anesthesia. With the lid everted on a chalazion clamp, and the conjunctiva prepared for operation, a small incision is made in the conjunctiva and the inferior tarsal ligaments along the lower border of the tarsal plate, usually in the center. The length of incision is usually 3 mm., but the amount of tissue to be removed is a matter of surgical judgment in each case. Small, blunt-tipped scissors are introduced through this opening to separate the tarsal plate from the orbicularis muscle in the region of the expected tarsectomy. In freeing the muscle from the plate, blunt dissection is used to avoid damage to the muscle fibers. This dissection is carried to the follicles of the cilia. Then a wedge of tarsus and conjunctiva is removed (figure). The base is the inferior border of the tarsal plate. The apex is carried almost to, but does not include, the palpebral margin. Little bleeding is encountered, as the vascular supply to the muscle has not been disturbed. In adults, fine interrupted black silk sutures are placed through the conjunctiva and the tarsal plate. In children, surgical gut is used. The knots are placed as low as possible to prevent contact with the cornea. A dressing is used for twenty-four hours, and the sutures are removed in ten to fourteen days.

The period covered in this preliminary work is not sufficient to determine the long range results of the operation, but it seems to be based on sound physiologic and anatomic principles. The operation is so simple that it can be performed in the office. It has the further advantage of producing no external scarring because the approach is from inside the lid. Also, this operation does not interfere with other lid procedures, as do the commonly performed Ziegler punctures or other cicatrizing operations. It has been so successful in the University of Oregon medical clinics that it merits a trial by various surgeons, with a diversity of cases, to determine whether it stands the test of time.

# PRACTICAL APPLICATION OF SURFACE-ACTIVE DRUGS IN OPHTHALMOLOGY

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## WETTING AGENTS

WITHIN the last twenty odd years there have been produced a number of synthetic chemicals analogous to soaps. These agents, like soaps, penetrate the "supposed tension of the surface" of any liquid but, unlike soaps, are not affected by hard water. The name "surface-active agents" has been given to these synthetic preparations.

The "Glossary of Physics"<sup>1</sup> gives this definition of surface tension:

... the peculiar effect of cohesion manifested at the free surface of a liquid or at the interface of two immiscible liquids, and giving the impression of a tense elastic skin membrane. It is measured in units of force per unit length, e. g., dynes per centimeter along the line on the surface.

A number of these surface-active agents have been prepared<sup>2</sup> to be used in such diverse industries as the manufacture of shampoos, dentifrices, inks, dyeing products, cosmetics, lubricating materials, the processing of leather, textile industries, air conditioning and fruit and vegetable peeling.

It is not necessary to mention that a great number of these products are much too acrid for use in ophthalmology. Many manufacturers are aware of this and warn against the promiscuous use of these products in medicine.

Johnson<sup>3</sup> and others have called attention to the fact that surface activity is not completely understood and that the phenomena of detergency in all its phases have not as yet been analyzed. However, a number of the surface-active agents have been checked on animals to determine any ill effect, thus: Hatton<sup>4</sup> fed irium, a sodium lauryl sulfate preparation with a small percentage of sulfated alcohols, in

1. Weld, L. D.: *Glossary of Physics*, New York, McGraw-Hill Book Company, 1937.

2. Young, C. B. F., and Coons, K. N.: *Surface Active Agents*, Easton, Pa., The Chemical Publishing Co., Inc., 1945, pp. 117-154.

3. Johnson, H. C. E.: *Scient. Am.* **174**:57, 1946.

4. Hatton, E. H., and others: *J. Dent. Research* **19**:87, 1940.

massive doses to rats without any untoward results. Gershenfeld and Wittin<sup>5</sup> gave massive doses of surface-active agents to rabbits intravenously and intraperitoneally for several months without any disaster. Several preparations have been used in dermatology.<sup>6</sup> Roth<sup>7</sup> suggested their use in ophthalmology.

Bellows and Chinn,<sup>8</sup> in experiments on animals, found a low percentage of chemotherapeutic agents in the aqueous after oral administration of the drugs. They stated the belief<sup>9</sup> that these sulfonamide drugs are better absorbed directly through the cornea. In later experiments on rabbits using chemotherapeutic drugs to the cornea with no wetting agents, satisfactory results were obtained.<sup>10</sup> At that time these observers suggested the use of these surface-active drugs in combination with mydriatics, miotics and antiseptics.

Theoretically, at least, surface-active agents should be ideal as vehicles for ocular medication, and with that thought in mind it was decided to check the foregoing data on human subjects.

#### BACTERIOLOGIC TESTS<sup>11</sup>

To assure ourselves that no deleterious effect would result from the use of any of these agents in our patients, it was decided first to recheck the animal experiments of surface-active drugs on rabbit eyes. A number of surface-active drugs were made up in 1 per cent solutions. Ringer's solution was used to make them isotonic. They were buffered to  $p_H$  7.3,<sup>12</sup> put up in 8 ounce (236 cc.) bottles, capped and left undisturbed for six months. They were then checked for sterility by inoculating 50 cc. volumes of culture mediums in fermentation tubes with 10 drops of each solution. The tubes were incubated for ninety-six hours at 37 C. Of the eleven solutions tested, triton X30® (sodium salt of aryl alkyl ether sulfate) and tween 80® (polyoxyalkylene ether

5. Gershenfeld, L., and Wittin, B.: *Am. J. Pharm.* **113**:215, 1941.

6. Duemling, W. W.: *Wetting Agents: New Synthetic Chemicals*, *Arch. Dermat. & Syph.* **43**:364 (Feb.) 1941. Goodman, H.: *Cosmetic Dermatology: Triethanolamine*, *ibid.* **36**:116 (July) 1937. Maynard, M. T. R.: *Triethanolamine: Adjunct to Dermatologic Therapy*, *ibid.* **25**:104 (June) 1932; *ibid.* **34**:268 (Aug.) 1936.

7. Roth, R. J.: *Am. J. Ophth.* **29**:717, 1946.

8. (a) Bellows, J. G., and Chinn, R.: *Arch. Ophth.* **25**:294 (Feb.) 1941.

9. Chinn, H., and Bellows, J. G.: *Corneal Penetration of Sulfanilamide and Some of Its Derivatives*, *Arch. Ophth.* **27**:34 (Jan.) 1942.

10. Bellows, J. G., and Gutmann, M.: *Application of Wetting Agents in Ophthalmology, with Particular Reference to Sulfonamide Compounds*, *Arch. Ophth.* **30**:352 (Sept.) 1943.

11. Mr. F. Wilson did the bacteriologic studies.

12. Feldman, J. B.:  *$p_H$  and Buffers in Relation to Ophthalmology*, *Arch. Ophth.* **17**:797 (May) 1937.

of partial oleic acid ester) were unsterile. Subcultures of blood agar plates revealed identical gram-negative bacilli in these two solutions. Saline suspensions of these organisms failed to produce any deleterious effect when introduced into the eye of a rabbit.

In the second batch of the same agents set up and examined in several days, the sterility tests, curiously, showed the same results as in the test cited above; i. e., triton X30® and tween 80® were again unsterile. From this observation, one would assume that the gram-negative bacilli must have been in the parent surface-active drugs, since the same parent wetting agents were used in making these identical dilutions six months apart.<sup>13</sup>

#### ANIMAL EXPERIMENTS

The animal experiments consisted in first instilling 3 drops of each solution into the eye of a rabbit, using a sterile pipet. The eye was observed at the time of instillation and at half-hour intervals over a period of three hours and on the following morning. On the following day the animals received two doses. The second dose was given three hours after the first. Unless it is mentioned, the same solution was used for the same eye of the rabbit throughout the study. Triton X135® and ultra-wet 30 DS® (an alkylated monosodium benzene sulfate) gave no apparent reaction at any time. These were therefore best tolerated; they comprised group 1. Group 2 consisted of triton X30® and tween 80®, which were not as well tolerated as the drugs in group 1. The rabbit eyes tested in this group consistently showed slight capillary congestion within two minutes after triton X30® and within five minutes after tween 80® was dropped into the eye. Nacconol N R S F® (sodium allyl aryl sulfonate) and ultra-wet E® gave even more congestion but, not appearing to be destructive to the corneal epithelium, were included in the second group.

The surface-active drugs which caused variable degrees of capillary congestion, chemosis, mucoid discharge and terminate edema were in the last group. In 1 case the pain caused the animal to squeal for a full minute after the instillation. These drugs comprised group 3 and included duponol C® (an alkyl sulfate), santomerse D® (an alkylated aryl sulfonate), tergitol penetrant 7 (a higher secondary alcohol sulfonate), C T A B® (cetyl trimethyl ammonium bromide) and aerosol O T (dioctyl ester of sodium sulfosuccinic acid).

For obvious reasons, group 3 was omitted from our clinical study on patients.<sup>14</sup> It is known that the rabbit eye is more sensitive than the human eye.

#### CLINICAL EXPERIMENTS

*Dosage.*—One of the purposes of using surface-action agents is that, since they are good wetting agents and should penetrate the cornea rapidly, only a minimal dose need be employed. The concentration of these ophthalmic drugs

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13. It was later decided that when these surface-active drugs were tolerated by the eye it was not necessary to alter their  $p_H$  or to make them isotonic.

14. Some of the solutions of surface-active agents were clear; others, slightly turbid; a few, even cloudy. No attempt was made to filter these solutions. It was found that the turbid solutions were slightly more painful than the clear ones but acted more effectively.

tested, therefore, was placed arbitrarily at 0.5 per cent, to be adjusted later as deemed necessary. Solutions of surface tension agents with atropine sulfate, paredrine hydrobromide ophthalmic<sup>®</sup> (1 per cent solution of *p*-hydroxy-*a*-methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2 per cent boric acid and preserved with merthiolate,<sup>®</sup> 1:50,000), pilocarpine hydrochloride, eucatropine hydrochloride, tetracaine hydrochloride, nitromersol N.F. (metaphen<sup>®</sup>) and homatropine hydrobromide were made.

*Records.*—The patient's name, age, color of iris and diagnosis were recorded, as well as the medication used, the intervals of instillation and the reactions obtained. When a mydriatic was used, an attempt was made to obtain the reaction to light, as well as to check the cycloplegic effect of the drug. The latter was affected by adding a +3 sphere to the refraction and by having the patient read .37 M type through a 3 mm. opening. Measurements were made with the Prince rule. This was done only with intelligent patients, when it was felt that rapid and trustworthy cooperation could be obtained. A number of patients were tested at the same period by the same combination of drug and surface-active agent, in order to determine whether or not the same therapeutic and beneficial effect was consistently obtained.

Finally, when a mydriatic was used, we recorded how long it took the pupil to return to normal with and without pilocarpine. It had been observed with previous mydriatics that the "blue iris" dilated fastest; the result was the same with our surface-active mediums. The color of the iris did not affect the burning or stinging after instillation of a surface-active agent.

*Examination of Patients.*—There remained, then, after the experiments with rabbit eyes, two groups of surface-active agents to be used on our patients. Group 1 included the preferred surface-active agents, triton X155<sup>®</sup> and ultra-wet 30 DS.<sup>®</sup> Group 2 included the agents to be used with some caution: triton X30,<sup>®</sup> tween 80<sup>®</sup> and particularly nacconol N R S F<sup>®</sup> (polyoxyalkylene ether of sorbitan and ultra-wet E<sup>®</sup> mono-oleate).

All surface-active agents bore a number unknown to us so that an unprejudiced opinion could be expressed when a preparation was used. Sometimes the same wetting agent was used on both eyes. Often the same drug in different wetting agents was used in the eyes of the same patient to determine the relative effectiveness of each surface-acting drug. Occasionally the same drug in many surface-active agents was used in the same eye in order to observe the cumulative effect of both the wetting agent and the ophthalmic drug.

Before any ophthalmic drugs were used, 50 patients were tried out with the surface-active agents of group 1 only. Having found no ill effect from the use of the wetting agents of this group, we tried paredrine and pilocarpine in combination with wetting agents of groups 1 and 2 in a series of 100 patients. After we found that the ophthalmic drugs were tolerated with surface-active agents, there were prepared solutions of 1 per cent surface-active agents with 0.5 pilocarpine hydrochloride, paredrine hydrobromide ophthalmic,<sup>®</sup> tetracaine (pontocaine<sup>®</sup>) hydrochloride, eucatropine (euphthalmine<sup>®</sup>) hydrochloride atropine sulfate, and homatropine hydrobromide, 0.5 and 1 per cent.

As before mentioned, the labels contained the name of the ophthalmic drug and a number only, signifying the wetting agent. With the patient's head tilted back, and with him looking down, single drops were instilled at the upper margin of the limbus. When a mydriatic was used, the patient was usually in a darkened room.



## OPHTHALMIC DRUGS

*Paredrine Hydrobromide Ophthalmic.*—Two hundred and fifty-one patients with ophthalmic disorders were examined (table 1). A large number obtained full dilation. Only 2 of these gave no reaction to light; all could read even though there was a maximum dilation, and none gave evidence of cycloplegia. The average time of full dilation was from thirty to eighty-seven minutes. One Negro woman,<sup>15</sup> aged 34, obtained full dilation with two instillations in eighty minutes. Another woman, white, aged 66, with hazel eyes and optic nerve atrophy, obtained full dilation, with ultra-wet 30 DS® for the right eye and ultra-wet E® for the left eye, in forty minutes. On the other hand, in about a dozen cases the pupil did not dilate to more than 6 mm. even though four or five instillations of the drug were given, up to seventy minutes in some cases.

TABLE 1.—Use of Ophthalmic Drugs in Wetting Agents

Ophthalmic Drugs, 0.5%	"Triton × 155"	"Ultra- Wet 30DS"	"Ultra- Wet E"	"Nacconol NRSF"	"Triton × 30"	"Tween 80"
Paredrine hydrobromide.....	57	55	32	28	38	41
Phocarpine hydrochloride.....	47	26	16	20	15	8
Tetracaine hydrochloride.....	19	23	7	..	..	..
Eucatropine hydrochloride.....	4	4	8	3	2	9
Homatropine hydrobromide, 0.5 %...	33	37	..	..	1	..
Homatropine hydrobromide, 1%.....	23	23	..	..	..	..
Atropine sulfate.....	15	14	14	2	10	10
Aqueous nitromersol.....	3	4	..	..	..	..

Of the various surface-active agents used, ultra-wet 30 DS® and ultra-wet E® gave a stinging sensation, and nacconol NRSF burned a great deal in a few cases. In some cases the first instillation burned but the succeeding drops did not.

To determine the relative merits of ultra-wet E® and tween 80® with 0.5 per cent paredrine hydrobromide ophthalmic®, we instilled the drops in the eyes of a large number of patients. It was found that ultra-wet E® gave the more severe pain. In fact, one elderly person had a mucoid discharge with a sensation of a foreign body for several days. Another elderly woman had chemosis with some edema; this woman had photophobia and a sensation of a foreign body for about three weeks.

In a woman aged 23 with hazel eyes, 0.5 per cent paredrine hydrobromide ophthalmic® in triton X30 was used for the right eye, and the same mydriatic in triton X155®, for the left eye. Four drops were instilled over a period of forty-five minutes, resulting in a 5 mm. pupil in the right eye and a 4 mm. pupil in the left eye. It is interesting that in

15. In Negroes, mydriatics of much higher potency are required to obtain full dilation.

this case triton X155,<sup>®</sup> which was previously known to be the least painful agent, was rather painful. Usually when the surface-active agents did produce pain, the physiologic effect of the associated ophthalmic drug was rapid. In this case, however, dilation was poor in the right eye. In the left eye, the entire epithelial layer of the cornea was denuded within forty minutes. There was photophobia, but not severe pain, with such blurred vision that none of the letters on the Snellen chart could be read. In several hours the epithelial layer of the cornea was reformed, but slight pain and photophobia prevented the patient from seeing the 6/60 line on the chart. The next morning she had 6/6 vision in each eye.

Not all patients had the same degree of corneal sensitivity. A woman of 25, with hazel eyes, received 0.5 per cent paredrine hydrobromide ophthalmic<sup>®</sup> in the right eye with the following surface-active agents: tween 80,<sup>®</sup> ultra-wet E,<sup>®</sup> nacconol NRSF<sup>®</sup> and, lastly, triton X30.<sup>®</sup> In the left eye there were instilled 0.5 per cent paredrine hydrobromide ophthalmic<sup>®</sup> in nacconol NRSF,<sup>®</sup> triton X30<sup>®</sup> (on three occasions) and, lastly, nacconol NRSF.<sup>®</sup> The drops were given over a period of eighty minutes. Except for a slight burning for five minutes after the first instillation of nacconol NRSF<sup>®</sup> to the left eye, there were no ill effects. There was full dilation of the pupil, but the eye still reacted to light and there was no cycloplegia.

Examination of a number of patients for tolerance and the mydriatic effect of paredrine proved that the surface-active agents were of value in the following order: triton X30,<sup>®</sup> ultra-wet 30 DS,<sup>®</sup> triton X155,<sup>®</sup> tween 80<sup>®</sup> and, lastly, ultra-wet E.<sup>®</sup>

*Pilocarpine Hydrochloride.*—The number of patients examined was 132. In most cases in which nacconol NRSF<sup>®</sup> was used the burning was severe and lasted for a considerable period. Very little pain was experienced with triton X30<sup>®</sup> and ultra-wet E.<sup>®</sup> No pain was felt with tween 80,<sup>®</sup> triton X155<sup>®</sup> or ultra-wet 30 DS<sup>®</sup>; yet when pilocarpine was given to patients for home use, the pain was so severe that the drug had to be stopped. This happened to 4 patients with refractory simple glaucoma. On the other hand, of an equal number of patients who were operated on for glaucoma (basal iridectomy), 3 had been using the same combination of 0.5 per cent pilocarpine hydrochloride to an ounce (30 cc.) of triton X155<sup>®</sup> for three months with no ill effects. Only 1 of these patients had to discontinue the medicine because of the severe pain experienced.

*Tetracaine Hydrochloride.*—Clinically, we observed that with 2 exceptions, tetracaine in a solution of a surface-active agent, gave pleasant, rapid and unquestionable anesthesia. This effect was explained

by Swan and White<sup>16</sup> as due to the pronounced lowering of surface tension by the tetracaine. In the 40 subjects tested, with the 2 exceptions to be noted, it did not make any difference which of our surface-active drugs was used.

Good anesthesia was obtained with triton X30® and ultra-wet 30 DS.® In a case in which tetracaine was used in nacconol NRSF,® the patient said, "For a while there was a sensation of a foreign body in the eye." In a second case, that of a young woman, an instillation of tetracaine in triton X155® produced a heavy mucoid discharge with much burning, the latter improving only after numerous irrigations of boric acid solution.

On the other hand, some patients were given tetracaine in a number of wetting agents to the same eye with no ill effects; for example, a patient received three instillations of several drops of tetracaine in triton X155,® ultra-wet 30 DS® and ultra-wet E® in each eye over a period of an hour, with no untoward symptoms.

*Eucatropine Hydrochloride.*—This drug was tested on 30 patients. All received from two to six instillations over a period of forty to seventy-seven minutes. The ages of the patients varied from 33 to 72 years. The pupils dilated from 5 mm. to a maximum of 7 mm. In 1 subject, an 8 mm. pupil was obtained. All the pupils reacted to light, and all the patients could read with maximum dilation.

*Homatropine Hydrobromine, 0.5 Per Cent.*—Seventy-one patients were studied. Full dilation was obtained in from thirty to ninety minutes. An exception was a 10 year old girl with brown eyes for whom eighty-five minutes was required for dilation to only 3 mm. in the right eye and to 4 mm. in the left eye.<sup>17</sup> Some patients obtained definite cycloplegia. In most patients the pupil did not react to light. In a few cases from two to five instillations were necessary to obtain full mydriasis.

After this study, 23 unselected subjects received 1 per cent homatropine hydrobromide in triton X155® in one eye and the same mydriatic in ultra-wet 30 DS® in the other eye, for comparative studies. It was found that homatropine hydrobromide in ultra-wet 30 DS® worked more efficiently. This finding applied to the 0.5 as well as to the 1 per cent solution.

Full mydriasis was obtained in thirty to eighty minutes with one or two instillations. Seven patients with fully dilated pupils had no cycloplegia and could read. Sixteen patients evinced definite cycloplegia. Two patients with 7 mm. pupils did not react to light and were

16. Swan, K. C., and White, N. G.: *Am. J. Ophth.* 25:1043, 1943.

17. It is possible that this poor mydriasis was due to the mydriatic's being flicked out because of pain caused by the wetting agent.

instructed to return later. In two hours the pupils were fully dilated, and, as previously noted, there was no reaction to light. They could not read, and they had definite cycloplegia. In some cases the pupils were dilated for twenty-four to thirty-six hours.

*Atropine Sulfate*.—Sixty-five patients obtained full mydriasis in from twenty-five to, in 1 case, eighty minutes. For the majority one hour was required. Two patients for whom nacconol NRSF<sup>®</sup> and triton X30<sup>®</sup> were used experienced a slight "scratching sensation." Because the children were very young, cycloplegia was not tested. An older child with a fully dilated pupil could make out the .37 M type. With several patients atropine was used in a surface-active agent for a week with no ill effect.<sup>18</sup> The dilation lasted about seven days in the majority of cases.

*Aqueous Nitromersol (Metaphen<sup>®</sup>)*.—Aqueous nitromersol (1:5,000) in triton X155<sup>®</sup> and ultra-wet 30 DS<sup>®</sup> was used in 7 cases. The pain was intense in each case. An effort to dilute the solution to 1:10,000, and even to 1:15,000, yielded no better results. On the other hand, a woman aged 70 with chronic dacryocystitis could not use a 1:10,000 solution and was advised to continue with the drug in spite of the pain. She persisted, and her eye improved. Of course, it might be that her condition would have improved, chronic conditions having periods of recession.

A dog's eye is the nearest approach to the human eye, the thickness of the dog's cornea being equal to that of the human. We were fortunate in securing a dog who had purulent conjunctivitis. A 1:10,000 aqueous solution of nitromersol was used alternately in triton X155<sup>®</sup> and ultra-wet 30 DS<sup>®</sup>. Both solutions pained a great deal and gave intense chemosis and edema of the lids. The solutions were stopped, and aqueous nitromersol (1:5,000) without a wetting agent was instilled, with complete recovery of this condition.

About the time our previous studies were completed, we were fortunate in obtaining several wetting agents not procurable previously. Among these were tween 80<sup>®</sup> and triethanolamine, U. S. P., both the commercial and the purer type,<sup>19</sup> sent directly to us by the manufacturer. The other wetting agents were hyamine L4-669,<sup>20</sup> a local antiseptic similar to benzalkonium chloride (zephiran chloride<sup>®</sup>), and several varieties of the tritons, varying in  $p_H$  from 8 to 9.

18. A number of these patients were from ophthalmic clinic at St. Christopher's Hospital for Children, Philadelphia.

19. The purer type is supposed to have less monoethylamine and diethylamine. We found the two types equally useful for our purposes.

20. J. L. Rainey, Ph.D., and L. H. Bock, Ph.D., of Rohm & Haas Company, Philadelphia, suggested the tests with these drugs.

Previously it was learned that a bland surface-active agent may become acid after the ophthalmic drug is added. To guard against this difficulty, the surface-active agents were checked in a 1 per cent solution on rabbit eyes and, in addition, were rechecked with the 0.5 per cent solution of the ophthalmic drug added to the wetting agent. Included in this study also were some ophthalmic drugs not previously used with ultra-wet 30 DS<sup>®</sup> or triton X155<sup>®</sup>. Also used were decresol OT (dioctyl ester of sodium sulfosuccinic acid), tergitol 4 and nacconol L.A.L.

#### ANIMAL STUDIES

*Method of Procedure.*—Three drops of the ophthalmic drug with the surface-active drug was instilled in the eye of a rabbit twice daily for two days. Observations were made at the time of administration and at one hour intervals during the day. A different eye was used for each medicament.

As a result of these studies, it was found undesirable to use fluorescein, mild protein silver, sulfathiazole and sulfadiazine in ultra-wet 30 DS<sup>®</sup>, but they were tolerated when used in triton X155<sup>®</sup>. We found that decresol OT<sup>®</sup>, tergitol 4<sup>®</sup> and nacconol L.A.L. were undesirable. We also discarded (1) paredrine in tween 80<sup>®</sup> (table 2); (2) pilocarpine in triton X200<sup>®</sup>; (3) homatropine dissolved in triton X500<sup>®</sup>, tween 80<sup>®</sup>, triethanolamine and triton X200<sup>®</sup> (table 2) and, (4) atropine dissolved in triton X500 and triton X720 (sodium salt of aryl alkyl polyether sulfonate). The rabbit eye showed no capillary congestion when these same ophthalmic drugs were dissolved in the other of this group of surface-active agents or when the antiseptic hyamine<sup>®</sup> L4-669 (1:10,000) was used.

#### LABORATORY STUDIES

EXPERIMENT 1.—At the time, it was thought desirable to observe what effect sulfathiazole would have on the aqueous concentration. Thus, two solutions were made up: one of 3 per cent sulfathiazole in triton X155<sup>®</sup> and another of 3 per cent sulfathiazole in water, as a control. Twenty-four doses of each solution were instilled in hourly doses during the day for a period of three days. Three drops was used in each instillation. After this period the aqueous fluid was removed from each anterior chamber, and a few hours later the secondary aqueous fluid was removed. Neither fluid contained sulfathiazole. It should be remembered that only triton X155<sup>®</sup> was used.

EXPERIMENT 2.—A dilution of hyamine L4-669 (1:10,000) was used with the test organism *Staphylococcus aureus*, FDA strain, in an agar cup plate. Six drops of incubation revealed a zone of inhibition of 3 mm. A portion of the agar in the clear zone was removed and

subcultured in broth. No growth was obtained after forty-eight hours of incubation, an indication that the action of the sample was germicidal. The phenol coefficient of the preparation is *Eberthella typhosa* 300; *Staph. aureus* 600. We dispensed this preparation to 20 patients, with good results in cases of catarrhal conjunctivitis and dacryocystitis.

#### CLINICAL STUDIES

Fluorescein, 0.5 per cent, in triton X155® was used on a number of patients; there was no pain, and the corneal abrasion showed up clearly.

*Paredrine Hydrobromide, 0.5 per cent, in Surface-Active Drugs.*—In 109 patients full dilation was obtained in from twenty-two minutes to two hours. Some patients did not have more than a 5 mm. pupillary opening. Some had no reaction to light, but many could read with full dilation. None had cycloplegia.

TABLE 2.—Further Study on Use of Ophthalmic Drugs in Wetting Agents.

0.5% Solution	"Triton* × 500"	"Triton × 155"	"Tween 80"	"Triton ethanol- A20"	Tri- amine	"Triton × 200"	"Triton 720"
Paredrine hydrobromide ophthalmic".....	15†	20	9† ‡	18	18	5†	24
Pilocarpine hydrochloride.....	22	33	28†	20	27	4† ‡	4
Eucatropine hydrochloride.....	4	5	5†	6	5	7†	6
Homatropine hydrobromide....	†	7	† ‡	9	†	†	12
Atropine sulfate.....	†	2	5	8	6	2	5†

\* "Triton × 500" is a clear, syrupy liquid, which when diluted to 1 per cent with distilled water becomes cloudy. This cloudiness, however, does not affect its efficiency.

† The eyes sting after a few instillations in some patients.

‡ The check on rabbit eyes showed from slight to considerable capillary congestion. In spite of this poor result in the rabbit, we used the drug on human eyes, with some stinging but without disastrous results.

Occasionally tween 80® and triton X500® gave a momentary sting when instilled in the eye. Possibly the most effective surface-active agents were in the order named: triethanolamine, triton 720® and triton A20.®

*Pilocarpine Hydrochloride, 0.5 per cent* (table 2).—One hundred and thirty-eight patients were examined. Previously, the pilocarpine had been poorly borne, especially when used in treatment of glaucoma, but not when used to contract the pupil after the use of a mydriatic. The results here obtained, however, were quite different. The patients included 12 patients operated on for glaucoma who were comfortable, except for a man, for whom triton X500® was used. This man had edema of the lids and severe pain, but he persisted in use of this drug for fourteen days despite the discomfort. The results with the other 11 patients were so encouraging that we even used pilocarpine in tween 80® in reducing ocular pressure, even though we knew from the

laboratory studies that the rabbit eyes showed capillary congestion after its use.

Contraction of the pupil and control of ocular pressure were best accomplished when triethanolamine, triton A20® and triton X200® were used.

*Eucatropine Solution, 0.5 per cent* (table 2).—Thirty-eight patients were treated with combinations of this drug. Even though the rabbit eyes were not affected by this combination, 3 of our 5 patients for whom tween 80® was used complained of pain. Some patients had instillations of all the seven combinations of surface-active drugs and eucatropine in each eye, with no ill effect.

Full dilation, but with reaction to light and ability to read, was obtained with only 1 patient, for whom triton X200® and tween 80® were used. This patient was 70 years old and had hazel eyes. Most patients, however, obtained a maximum pupillary diameter of 4 to 5 mm.

*Homatropine Hydrobromide, 0.5 per cent*.—There were 28 patients in this group. Because it was felt that homatropine would be difficult to neutralize if there were severe congestion, it was decided not to use a solution of this drug in the surface-active agents which demonstrated conjunctival irritation in the rabbit eye (table 2).

The rapidest dilation was obtained with the following wetting agents, in the order indicated: triton 720®, triton A20® and, lastly, triton X155®. Full dilation was obtained in from thirty to fifty-seven minutes. A few patients showed reaction to light, and several could read in full mydriasis. Three gave evidence of cycloplegia. Three drops was the greatest number used.

*Atropine Sulfate, 0.5 per cent*.—Twenty-eight patients were treated with combinations of this drug. The results were not encouraging. It is possible that, since the dose was small (0.5 per cent) and atropine takes a long time to act, the first drop has spent itself before the second drop was instilled. It was much more difficult to obtain full dilation with this drug than with homatropine.

Of the few wetting agents in this group, possibly the best results were obtained with tritons X200®, X155® and A20®. In 1 case, triton 720® instilled in one eye and triton A20® in the other gave full dilation in twenty minutes. In some cases there was no reaction to light and the patient could not read. On no case could a test for cycloplegia be made. The patients for whom atropine was used had a corneal ulcer or iritis or their cooperation was unreliable because of their extreme youth.

#### SUMMARY AND CONCLUSIONS

Surface-active agents are often called wetting or penetrating agents. Because of these qualities, they were suggested for use as vehicles, in common with many ophthalmic drugs.

There are over a thousand of these preparations now in use, and they are suitable for a host of purposes, from toothpastes to automobile greases. A large majority are much too irritating to be used in ophthalmologic practice.

To evaluate these drugs, we tested a number on rabbit eyes, and then on patients. We also checked the agents bacteriologically to determine their bacteriostatic action. It was found that certain wetting agents had no deleterious effect on the eye, but became irritating only when combined with certain ophthalmic drugs.

A new preparation, hyamine L4-669,<sup>®</sup> similar to benzalkonium zephiran<sup>®</sup> chloride, was proved to be valuable as an antiseptic by laboratory and bacteriologic studies and by clinical use in treatment of infections in the human eye.

A 3 per cent solution of sulfathiazole in triton X155<sup>®</sup> instilled in the eye of a rabbit at frequent intervals for several days did not appear in the primary or the secondary aqueous. An effort will be made to repeat this study with other surface-active agents. Over 1,000 patients have been studied.

A 1 per cent solution of the surface-active agent as a vehicle was used with such drugs as 0.5 per cent atropine sulfate, homatropine hydrobromide, eucatropine hydrochloride, tetracaine hydrochloride and paredrine hydrobromide ophthalmic.<sup>®</sup> Many proved fairly effective. The relative therapeutic effect of the various combinations is given. Good results appear to be obtained when the  $p_H$  of the surface-active agent ranges from 8 to 9.

At present no method of standardizing surface-active agents is known, and one batch of material may differ slightly from another. This difficulty will be overcome in due time.

The new mydriatic dibutoline sulfate (dibutylcarbonate of dimethyl-ethyl-2-hydroxyethylammonium sulfate), 5 per cent, is surface active. The effectivity of tetracaine has been explained by its surface activity.

Recently, Hauser and associates,<sup>21</sup> in their work with sodium penicillin, called attention to the fact that this preparation is surface active—a property which possibly accounts for the excellent results obtained by its use. Chemical manufacturers are usually cooperative, and it is felt, with their assistance, a large number of vehicles will become available for use in ophthalmology.

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21. Hauser, E. A.; Phillips, R. G., and Phillips, J. W.: *Science* **106**:603, 1947.



## OPERATION FOR CONGENITAL CATARACT

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THE SUBJECT of congenital cataract is given relatively little space in textbooks of today. The traditional treatment of needling or discission, often repeated, is generally employed. Needling is open to many serious objections, such as the danger of chemical irritation and secondary glaucoma, which not uncommonly necessitates further operation on a highly inflamed eye. Other objections are protracted convalescence; the frequent necessity of repeated discission in order that resorption may be complete, and delayed restoration of vision in young subjects, with resultant amblyopia. Retinal detachment not uncommonly occurs in adult years as a result of repeated discission in early childhood. Ziegler recommended the through and through incision, hoping to prevent secondary glaucoma. According to Spaeth,<sup>1</sup> a through and through incision of the lens into the vitreous is not a guarantee against the development of secondary glaucoma; instead, damage may occur to the vitreous, with later development of iridocyclitis of chronic type, and even retinal separation.

Elschnig<sup>2</sup> recommended removal of the lens by "linear extraction" at the age of 3 months for the relief of total cataract and at the age of 6 months or later for partial cataract. Because of its danger, "linear extraction" was not generally accepted. A technic of "linear extraction," modified to avoid the danger and to permit safe removal of congenital (and membranous) cataract in infancy, as well as later, was suggested by me<sup>3</sup> in 1931. Its favorable aspects were confirmed by Green and Beisbarth.<sup>4</sup> Additional

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2. Elschnig, A.: Graefe, A., and Saemisch, T.: *Handbuch der gesamten Augenheilkunde*, ed. 2, Leipzig, W. Engelmann, 1908, p. 1192.

3. Barkan, O.: A Procedure for Extraction of Congenital, Soft and Membranous Cataracts, *Am. J. Ophth.* **15**:117-124 (Feb.) 1932.

4. Green, J., and Beisbarth, C.: Extraction of Congenital and Young Adult Traumatic Cataract by the Method of Barkan, *Am. J. Ophth.* **16**:603-606 (July) 1933.

modifications which have since been introduced are described in the present article. The essence of the procedure is to dilate the pupil maximally with atropine instilled for four days prior to operation and again with epinephrine hydrochloride U. S. P. (1:1,000) injected sub-conjunctivally at operation. Thus the margin of the pupil comes to lie peripheral to the inner lip of the wound of the keratome incision. The incision is made obliquely in the cornea 1 to 1.5 mm. axial to the corneoscleral border, and in a plane parallel to that of the iris. Designed as a trapdoor, or valve, incision, which is watertight and airtight as regards the contents of the anterior chamber, it prevents the outflow of fluid or air and encourages rapid reformation of the chamber. This effect, combined with maximal dilation of the pupil and the hypotony induced by epinephrine (dynamic, since it is due partly to stimulation of the sympathetic nerve fibers), tends to prevent the iris from contacting or adhering to the inner lip of the wound. Since anterior adhesion of the iris occurred, nevertheless, in some cases, a precautionary measure was instituted. This consists of post-operative reestablishment of the anterior chamber by means of injection of isotonic sodium chloride solution through a prelaid corneal puncture. The patient leaves the operating table with the chamber fully reformed. Since this modification has been added to the original procedure there has been no instance of anterior adhesion. Dr. F. C. Cordes recently reported the injection of a bubble of air after operation for the same purpose. The bubble is so placed by positioning of the head that contact of the iris with the inner lip of the wound is less likely. Introduction of the bubble of air may be combined with the injection of saline solution.

In case a secondary membrane forms, it is suggested that needling or discission be avoided. If the membrane is delicate, it may be removed by gentle traction with the smallest type of capsulectomy forceps. If thick and tightly adherent, it may be cut at right angles to the line of traction with Barraquer scissors. Both maneuvers can be performed with a high degree of safety by the surgical technic already outlined.

The absence of complications and the smooth convalescence are in striking contrast to the delay and complications of discission. The establishment of clear media in early infancy is advantageous. No late complications, such as retinal detachment, has been encountered. There has been no case of sympathetic ophthalmia.

In the case of binocular total cataract it is suggested that surgical intervention begin when the infant is 3 months of age. After successful surgical treatment of one eye, the other eye should be operated on without delay. In my experience, corrective glasses have been worn after operation with satisfaction in several cases at the age of 4 and

5 months. Since experience has shown that no useful purpose is accomplished by early operation in cases of monocular cataract, it is recommended that surgical treatment be deferred in such cases until a later age, when full cooperation of the patient is obtainable.

#### SURGICAL PROCEDURE

A drop of 1 per cent solution of atropine sulfate is instilled in the eye to be operated on once a day for four days. Examinations, including a roentgenographic study of the chest for enlargement of the thymus, are carried out in all cases. With

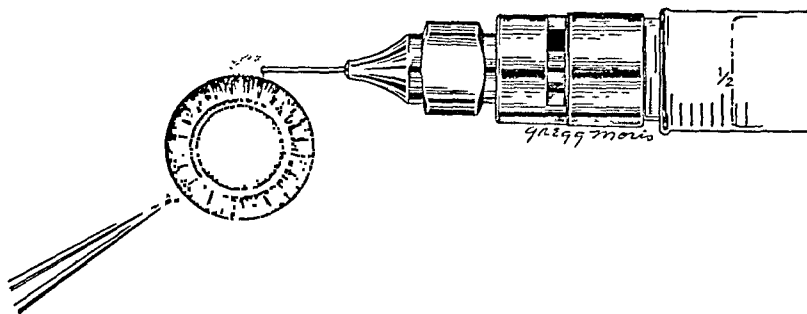


Fig. 1.—Injection of epinephrine hydrochloride U. S. P. (1:1,000).

infants the usual diet is maintained up to six hours prior to operation; sugar solution is forced up to four hours to avoid dehydration with associated hyperpyrexia.

General anesthesia is used with infants and with children of ages up to 12 or 14 years. In view of the delicacy of the operation as applied to infants who may be only a few months old, and who may show other congenital defects, the importance of the anesthesia cannot be overemphasized. An injection of atropine is given forty-five minutes before operation. Ether is administered through a

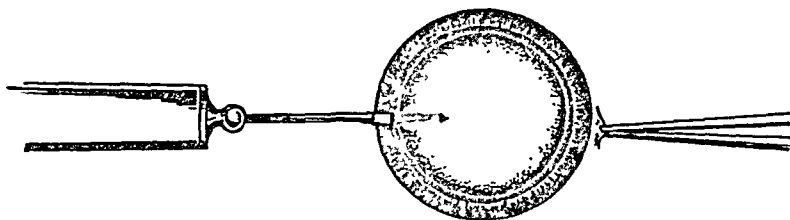


Fig. 2.—Corneal puncture.

suitably small airway. Since the face is covered with an eye sheet and the operation may prove lengthy, a generous supply of oxygen should be assured at all times.

Before the operator scrubs and the patient is draped, 2 to 4 minims (0.124 to 0.248 cc.) of epinephrine hydrochloride U. S. P. (1:1,000) is injected at several points along the upper limbus with a no. 30 needle  $\frac{1}{2}$  inch (1.27 cm.) in length (fig. 1) attached to a  $1\frac{1}{2}$  inch (3.8 cm.) Luer syringe. The intraocular action is increased by injecting as close as possible to the corneoscleral border. The injection is facilitated by inserting the needle with the opening facing the bulbus when puncturing the conjunctiva. It is best to inject the major portion at 12 o'clock in the meridian contiguous to the point of corneal incision. Akinesis is

induced and a retrobulbar injection of 2 per cent procaine is given and the eye is prepared in the usual manner. The face mask should be of moistened gauze in order that it may be easily molded to the region.

After ten to fifteen minutes the pupil is maximally dilated, so that it almost disappears behind the limbus and hypotony has developed. The dilation, being due to a contraction of the sympathetic dilator fibers, is tonic, in contradistinction to the paralytic dilation of atropine. The iris consequently maintains an exaggerated contractility, which keeps it retracted from the wound and prevents its prolapse. The hypotony of the bulbus induced by epinephrine is such that the usual tendency of the ocular contents to prolapse is greatly reduced. This tendency is further discouraged by making the keratome incision oblique and within the cornea.

Adequate exposure is provided by canthotomy and by lid sutures, six to eight in number, of 000000 black silk placed along the ciliary margins of the upper and lower lids. The sutures are held with mosquito forceps. The superior rectus is controlled by a bridle suture of 000000 black silk.

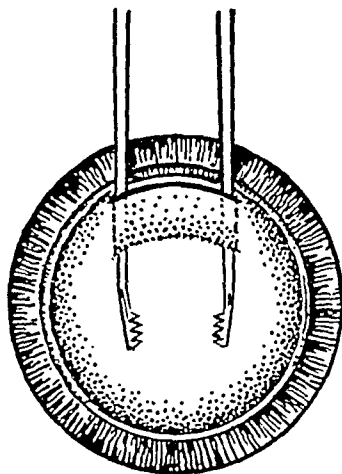


Fig. 3.—Corneal incision and capsulectomy forceps

Illumination and magnification are important. In the cases of membranous cataract, the focal illuminator will eliminate annoying reflections.

A corneal puncture is made in preparation for the later deepening of the anterior chamber, the blade being placed extremely tangentially, 1 mm. axial to the corneoscleral border at 9 o'clock on the right eye and at 3 o'clock on the left eye, after the site has been touched with an applicator previously dipped in tincture of iodine (fig. 2). A discission knife which has been dipped in fluorescein to mark the position of the puncture is used, the bulbus being fixed by a Bishop Harman forceps at the opposite limbus. The wound canal should be at least 2 mm. long, so that it will be air and water tight. The tip of the knife should barely perforate Descemet's membrane, as observed through a head loupe. It may be necessary to tip the blade backward a little in order to perforate the membrane. Care should be taken not to enlarge the puncture on removing the knife.

The corneal incision is made with a keratome at 12 o'clock, 1 to 1.5 mm. axial to the corneoscleral border. It is placed obliquely to the corneal surface and parallel to the plane of the iris, thus forming a valve, or trapdoor, incision, which tends to close more tightly, the greater the pressure within the anterior chamber. It should be no larger than necessary for the extraction of the lens

matter or membrane, as the case may be. Excessive obliquity may interfere with freedom of intraocular instrumentation, but the size and obliquity can be adapted to the needs of the individual case in order to achieve an optimum of freedom of instrumentation, deliberate manipulation, security of healing and elimination of hazards (fig. 3).

A number of instrumental procedures have been described for the extraction of the various forms of congenital cataract and membranes. It is beyond the scope of this paper to more than touch on them. Depending on the type of cataract or membrane to be operated on and the individual operator's preference, capsulectomy forceps, cystotome, narrow Hess shovels, irrigation, blunt hook or small, delicate Barraquer scissors may be used. The various types of congenital cataract and their surgical implications have recently been described in a comprehensive review of the subject by Dr. Cordes.<sup>5</sup>

At the end of the operation the anterior chamber is deepened in the following manner: The corneal puncture, which was prelaidd with a discission knife and stained with fluorescein, is touched with a dry applicator and with one dipped in tincture of iodine. With a no. 30 needle (previously drum tested or examined under a loupe to assure its having a perfect point) attached to a 1.5 cc. Luer syringe, saline solution is injected, the surgeon fixing the bulbus at the contralateral portion of the limbus (fig. 4). Air may be injected in the same manner.

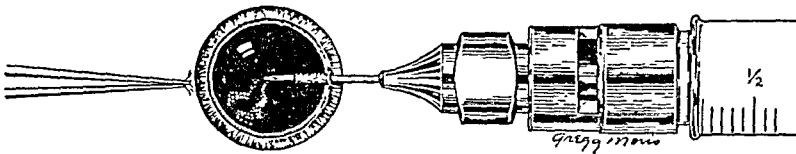


Fig. 4.—Deepening of the anterior chamber.

It is important for the patient to leave the operating table with the anterior chamber deep.

The usual measures for postoperative care, consisting of use of binocular pads, eye shield and arm restrainers, are observed. Elixir of phenobarbital is administered.

#### SUMMARY

The traditional treatment of needling or discission of congenital cataract or membrane is open to many serious objections. Removal of the cataract by a modified form of linear extraction is recommended. The technic is described. Recent modifications are given which further assure extraction without hazard in early infancy.

490 Post Street (2).

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## CHOROIDORETINAL DEGENERATION

### A SEX-LINKED FORM IN WHICH HETEROZYGOUS WOMEN EXHIBIT A TAPETAL-LIKE RETINAL REFLEX

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THE TAPETUM lucidum, an iridescent cellular or noncellular layer of the choroid, which is responsible for the metallic reflex seen at night in the eyes of many mammals, is not present in the human eye. However, in rare instances a tapetal-like retinal luster has been observed ophthalmoscopically. In the 2 cases described by Mann<sup>1</sup> the abnormality occurred in women and was unaccompanied with any impairment of vision. Concerning one of these women, it was said that in childhood "her eyes used to glow in the dark like an animal's." Dr. Mann's patients were not known to be related, and their families were not investigated.<sup>2</sup> To our knowledge, only 1 other instance of a tapetal reflex has been mentioned in the ophthalmologic literature, this being the case of a woman described by Niccol.<sup>3</sup>

During the course of a genetic study which originated with a 30 year old man who exhibited an atypical form of retinitis pigmentosa, an unusual appearance of the fundus was discovered in the man's mother and in one of the latter's sisters. The anomaly seen in these women closely resembled that described by Mann<sup>1</sup> in the case represented by her figure 105. Further investigation revealed the occurrence of additional cases of both retinitis pigmentosa and the tapetal-like condition in such a way as to suggest the operation of a sex-linked gene producing retinitis pigmentosa in males and the tapetal-like reflex in heterozygous females. Because of practical, as well as theoretic, interest attaching to this unusual form of eyeground, it is proposed to describe the family in detail.

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Support for this study was provided by the Board of Governors of the Horace H. Rackham School of Graduate Studies, University of Michigan.

From the Department of Ophthalmology of the University Hospital and the Heredity Clinic, Laboratory of Vertebrate Biology, University of Michigan.

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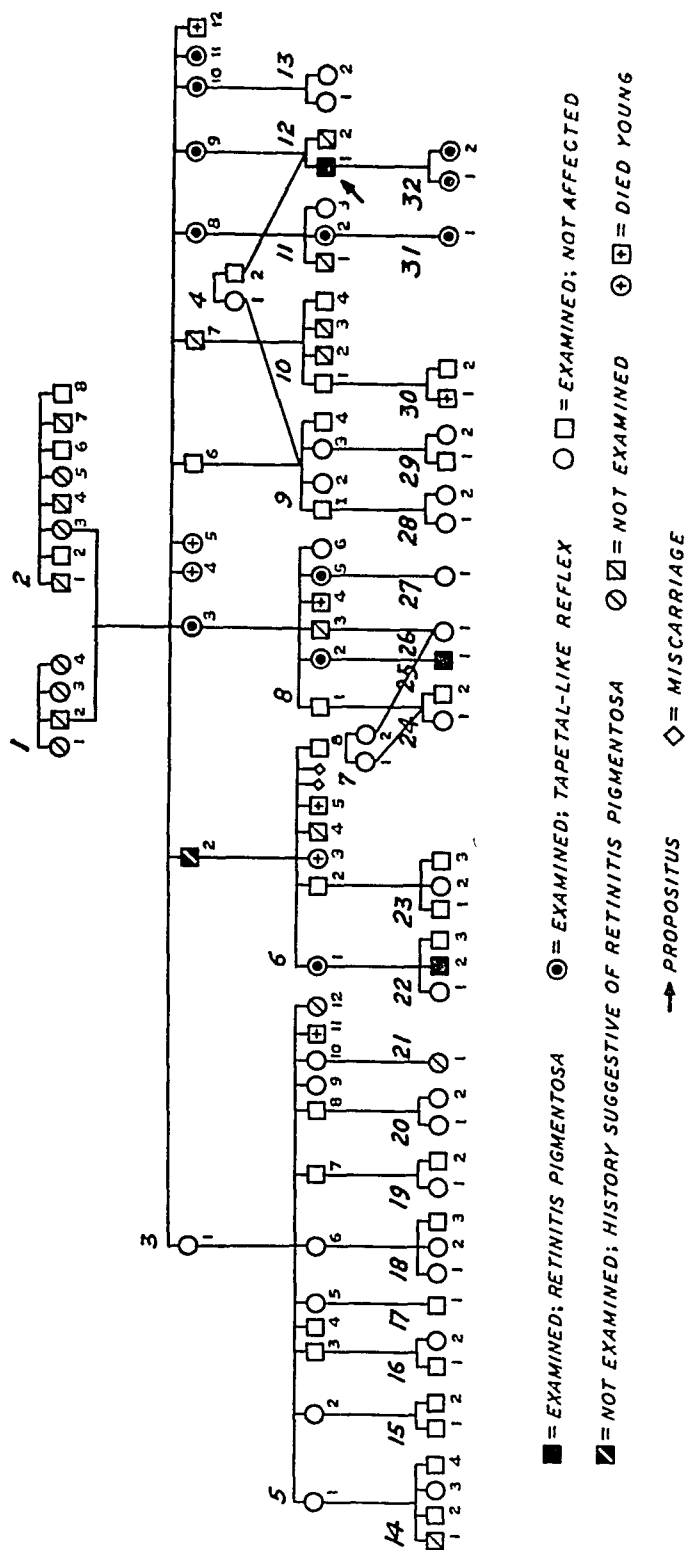


Fig. 1.—Heredity chart of kindred 776 of the Heredity Clinic of the University of Michigan, showing a sex-linked form of choroidoretinal degeneration in which heterozygous women exhibit a tapetal-like retinal reflex.

This family constitutes kindred 776 in the files of the University of Michigan Heredity Clinic. The pedigree presented in figure 1 shows 105 relatives of the propositus, of whom 75 were examined in their homes or at the ophthalmic clinic of the University Hospital. The spouses of these subjects were also examined in almost all cases and were found to be normal with respect to the two abnormalities under study. The spouses have therefore been omitted from the pedigree chart except in cases in which they were known to be related *inter se*, producing double first cousin relationships. In the following sections of the paper, each individual member will be identified by means of a double number, the first number designating the sibship, as indicated by the number above the sibship line in figure 1, and the second designating birth order within the sibship, as shown by the number beneath the individual's pedigree symbol. Thus, the propositus, or original patient, is 12-1, and, as is seen in figure 1, his daughters are 32-1 and 32-2. The spouses will be identified by adding the letter *a* to the number of the espoused. Thus, the wife of 12-1, who is not shown in the diagram, will be designated as 12-1*a*.

On the hypothesis of sex-linked inheritance, the gene responsible for the disease present in this family must have been derived from 2-3, the mother of sibship 3. Beyond this point its origin is problematic. Three of 2-3's brothers, 2-2, 2-6 and 2-8, were living. Examination of these men revealed good visual acuity, normal color vision and absence of fundic changes suggestive of retinitis pigmentosa or related defects. Numerous descendants of 2-1, 2-2, 2-4, 2-6 and 2-8 were examined, without further trace of the two anomalies in question. Only 1 member of sibship 2 was reported to have had "bad eyes," namely, 2-7. He was said to have been extremely near-sighted from childhood, but he did not complain of night blindness; he died at the age of 50, leaving no children. The parents of sibship 2, C. P. (father) and W. E. (mother), resided near Breslau, Germany. After the latter's death the family emigrated to America, settling in Brown County, Wis.

#### SUMMARY OF OCULAR FINDINGS

A description of the ocular histories and abnormalities of the fundus of the propositus (12-1) and his mother (3-9) will be presented first. The left fundus of 12-1, showing retinitis pigmentosa, is depicted in figure 2*A*, while the corresponding fundus of a maternal aunt (3-10), showing the typical glistening golden verruciform, or "tapetal-like" change, is shown in figure 2*B*. In these 2 subjects, as in other affected members of the kindred, the two eyes were rather symmetrically involved. However, interesting variations were observed between the eyes of various other affected persons, and we shall therefore add somewhat briefer descriptions of the other affected members. In addition,



a few cases will be cited in which we encountered ocular abnormalities which were probably unrelated to the disease under investigation. These cases will serve to illustrate the fact that examination of any large kindred is likely to disclose a variety of ocular anomalies, which might easily lead to erroneous genetic interpretation if hearsay information alone were accepted.

12-1.—O. P., a man aged 30, who served as the proband for the family investigation, was first seen at the University of Michigan Hospital on Dec. 11, 1945. His chief complaints were night blindness and ease of ocular fatigue. The patient's uncorrected visual acuity was 2/60 in each eye. With his own correction visual acuity was 6/30 in the right eye and 6/15+1 in the left eye. External ocular examination showed a normal condition except for an alternating divergent strabismus, which measured 10 degrees (Priestley Smith). The pupillary reflex was normal in both eyes. The irides were blue with considerable brown around the pupillary margins.

Fundus examination revealed a small area of centrally placed posterior subcapsular cataractous change in each lens. There were numerous opacities in the vitreous. The optic disk in each eye was somewhat indistinct, as a result of moderate glial infiltration. The choroidal circulation was vividly seen throughout the entire fundus in each eye. It was most conspicuous in the vicinity of the optic nerve head and at the retinal periphery. Not illustrated in the drawing (fig. 2A), but visible ophthalmoscopically, were a few choroidal vessels showing evidence of early sclerotic change. The retinal arteries and veins were both somewhat reduced in caliber. There was no evidence of arteriolar sclerosis. As shown in figure 2A, the pigment in the immediate vicinity of the fovea and the macula retained some of its normal characteristics, except for stippling and mottling. Temporal to the disk the pigment was clumped in small, irregular masses. The entire retina, with the exception of the macula, was conspicuously atrophic. The retinal pigment had migrated into the substance of the retina and had become arranged in strands and clumps. In some areas it had apparently piled up in the perivascular spaces. The fundi were very similar except for minor variations in deposition of pigment.

With standard clinical illumination and a 5/330 test object, the visual fields were found to be concentrically constricted to within 5 degrees of the fixation point. Color vision was normal (Ishihara, seventh edition). Tonometric tension was 24 mm. of mercury bilaterally (new Schiøtz method).

Refraction gave the following correction: right eye:  $-2.75$  sph.  $\ominus -2.00$  cyl., axis 11, vision 6/30; left eye:  $-2.25$  sph.  $\ominus -2.50$  cyl., axis 172, vision 6/15+. Measurements of muscle function showed 3 degrees of left hyperphoria for distant vision (right eye) and 2 degrees of left hyperphoria with 16 degrees of exophoria in accommodation (left eye).

3-9.—Mrs. E. H. P., the mother of the proband, was first examined at the age of 47, when she accompanied her son on one of his clinical visits. She specifically stated that she did not have trouble with vision in the dark, but complained of minor asthenopic symptoms. On Jan. 22, 1946 visual acuity was 4/60 in each eye. Refraction with paredrine and homatropine cycloplegia gave the following correction: right eye:  $+4.25$  sph.  $\ominus +1.25$  cyl., axis 92, vision 6/6; left eye:  $+4.25$  sph.  $\ominus +1.25$  cyl., axis 90, vision 6/6. Measurements of muscle function revealed a minimal convergence insufficiency. The irides were blue with brown pupillary borders. The remainder of the external ocular examination revealed nothing significant.

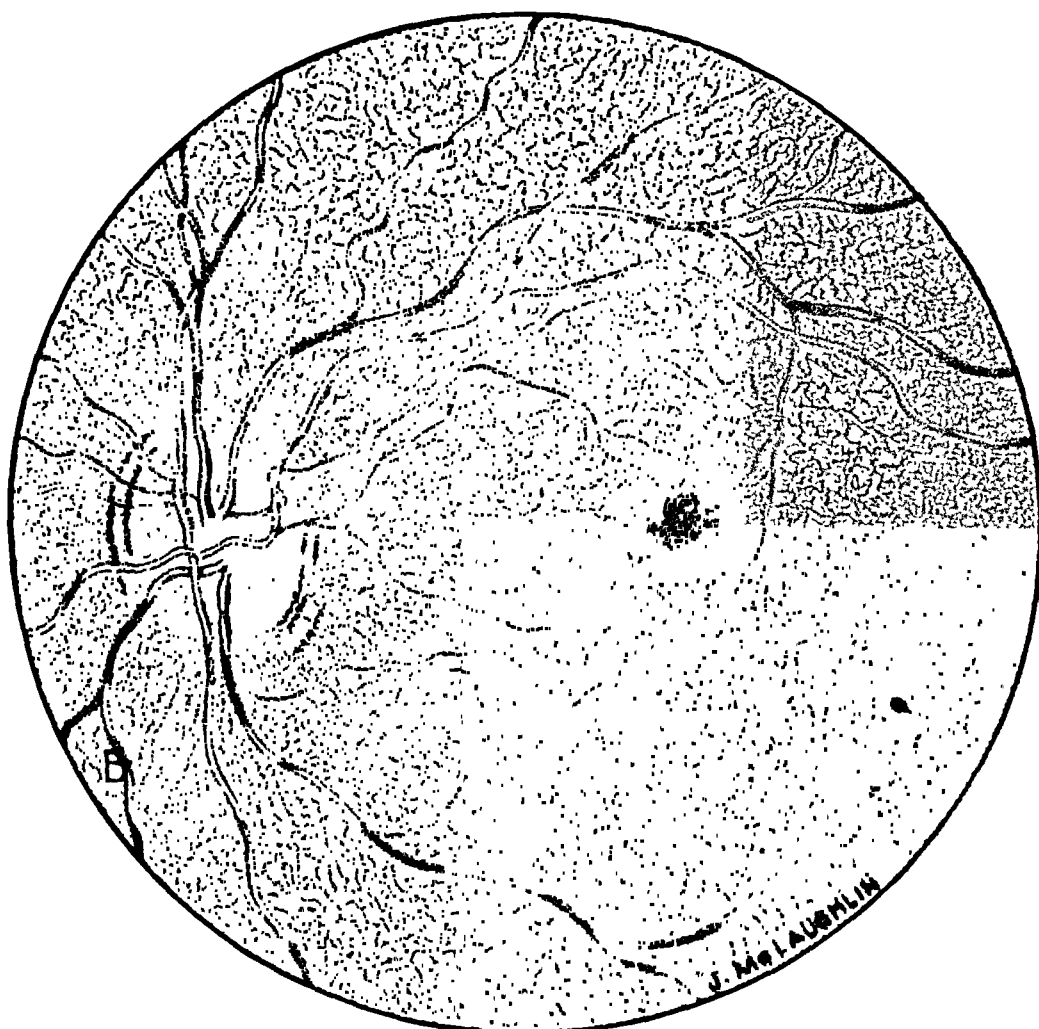
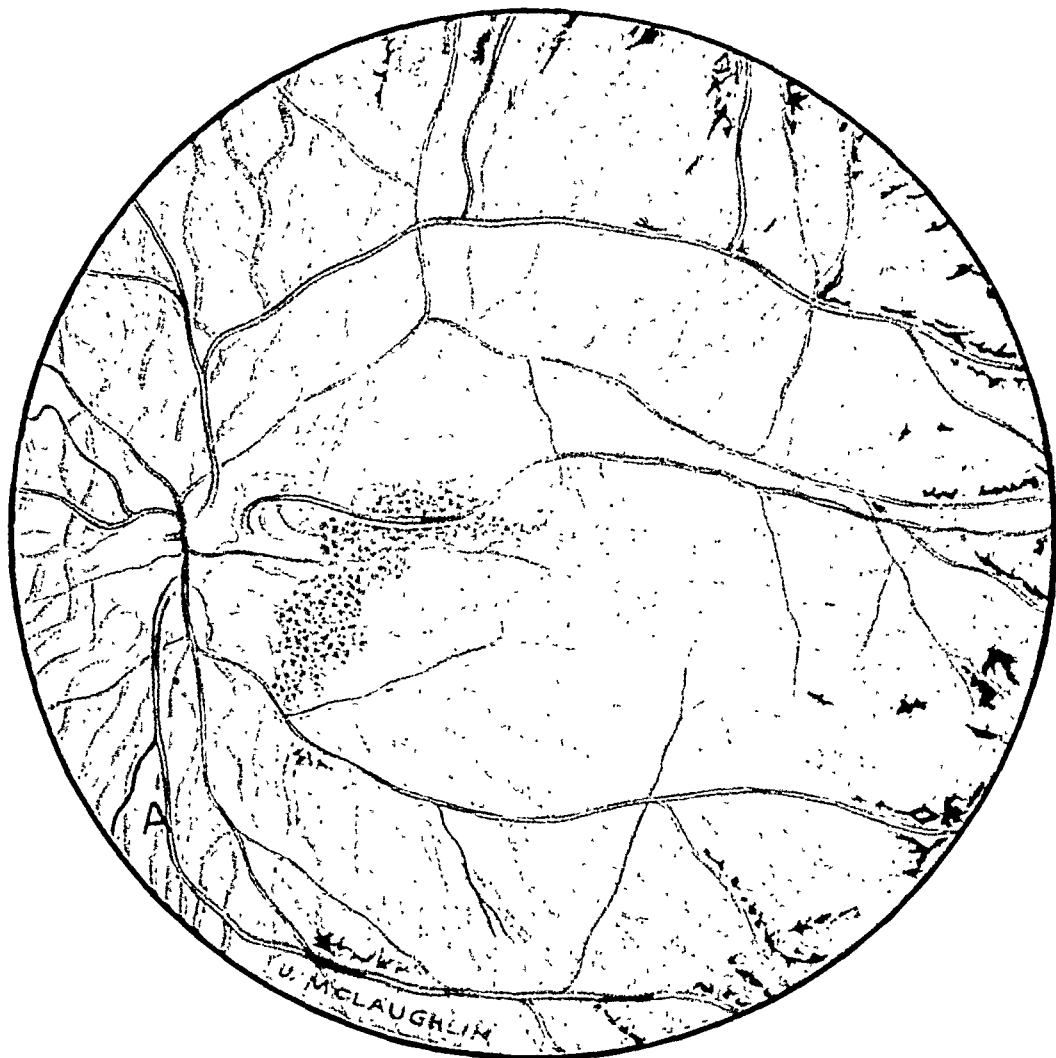


Fig. 2.—*A*, left fundus of 12-1, showing retinitis pigmentosa; *B*, left fundus of the maternal aunt (3-10), showing the tapetal-like change.



Fundusoscopic examination showed that the lens and central media were clear in both eyes, except for a few strandlike opacities in the vitreous. The disks were normal in size and color and were oval vertically. The retinal vasculature was normal except for a slight reflex striping of the arterioles. There was a good foveal reflex in each eye, and the macular pigmentation was normal. However, scattered in and about the macular area were numerous dustlike, golden, glittering bodies. With the binocular ophthalmoscope these bodies were seen to be deep to the retinal vessels and seemingly were obscured by the increased pigmentation at the macular center. Because of these two features, it was concluded that they probably represented minute verrucae or drusen. They were so numerous in specific areas as to become conglomerate and apparently formed irregular masses. When specific details were not fixated, the impression was that of a golden yellow sheen, not unlike that seen in certain mammalian fundi. The verruciform structures were most numerous just outside the macular area and faded out gradually into the retinal periphery. There was no suggestion of a pathologic condition of the retina except for the presence of occasional small areas of depigmentation in the extreme periphery. There was no essential difference between the two fundi.

Tonometric tension was 21 mm. of mercury bilaterally (new Schiøtz method). Visual fields, measured in the usual clinical manner with a 2/330 test object, showed a minor contraction of the field temporally and inferiorly in each eye. The blindspots were normal in size, and there was no evidence of central scotoma. Color vision was normal (Ishihara). The Kahn reaction of the blood was negative.

1-2.—W. H., the elder, the maternal grandfather of the propositus, had died at the age of 89, in 1945. According to his relatives, he first complained of loss of vision at the age of 60, but no statements concerning night blindness could be recalled. During the last three or four years of life he was said to have been totally blind. Dr. E. S. Schmidt, of Green Bay, Wis., furnished us the following facts: "Mr. W. H. consulted me on Jan. 22, 1919, with vision of 8/200 in the right eye and of 5/200 in the left eye. At that time he complained of seeing through a fog all the time. The disks were pale and had a pearly look." No other abnormalities were visualized in the fundi at that time. A Wassermann test was not performed. It was Dr. Schmidt's impression that the patient had primary atrophy of the optic nerve of unknown cause. In accordance with the mode of inheritance postulated here, i.e., sex linkage, he would not have been expected to possess retinitis pigmentosa, inasmuch as he possessed a daughter (3-1) lacking the heterozygous manifestation and a son (3-2) who was presumably affected.

3-2.—W. H., the younger, had died at the age of 56, in 1942, and information concerning him was obtained solely through his wife and a local optician. The latter possessed a pair of glasses worn by the patient containing a —6 D. sphere for the right eye and a —8 D. sphere for the left eye. According to his wife, he had been sent home from school at the age of 10 because he needed glasses. Vision failed progressively, and during the last years of life he was said to have been almost totally blind, being able to see objects only when they were directly in front of him. He consistently refused to consult an oculist. On the pedigree chart (fig. 1) we have chosen to regard him as probably affected with retinitis pigmentosa.

3-3.—Mrs. P. J. P., a moderately obese woman aged 61, was the oldest woman examined among the known carriers, or heterozygotes. An unusual amount of melanin pigment was present in the skin of the eyelids bilaterally. There was considerable scarring of the face, which was attributed to roentgen burns resulting from treatment for hirsutism of the upper lip. She had never worn glasses and

expressed no difficulty with reading or ocular discomfort of any kind. Uncorrected vision was 6/9 in the right eye and 6/12 +1 in the left eye. External ocular examination was noncontributory except for moderate lateral deviation under cover and minimal arcus senilis bilaterally. The central media were clear except for occasional opacities in the vitreous. The disks were normal, but a moderate degree of circumpapillary retinal atrophy was present. A good foveal reflex was noted in both macular areas. The typical verruciform golden appearance of the fundus previously described was present. It differed from that to be described for the patient's younger sisters in that the supposed verrucae were somewhat larger, and possibly less numerous. The retinal arterioles showed mild, sclerotic changes, but no unusual degree of choroidal arteriosclerosis could be seen. The retinal periphery disclosed a few scattered areas of depigmentation, bordered by thin rings of accumulated pigment. There was no evidence of inflammatory disease. In the confrontation test, the fields showed minimal peripheral constriction, which was slightly more pronounced in the left eye. Subjectively, however, the patient was unaware of any handicap in the dark, as in walking about the yard at night or on entering a dark moving picture hall in the daytime.

3-8.—Mrs. B. D., a blonde woman aged 50, had no ocular complaints. Uncorrected visual acuity was 6/9 —1 in each eye, and she could easily read ordinary newsprint with a +2.00 spherical lens. The skin of the lids was finely wrinkled and somewhat thin for a woman of her age. Some minor facial asymmetry was present, the left orbit being slightly higher than the right. The left half of the face was also noticeably narrower than the right. The cover test disclosed exophoria. Mild arcus senilis was seen in both corneas. The anterior chambers, irides and pupillary reflexes were normal. The central media were clear. The disks showed high central branching with structural blurring of the margins. The foveal reflex was well seen in both eyes. Extensive minute verrucae, so fine and conglomerate as to give the impression of gold dust, were seen throughout the fundi, except in the extreme retinal periphery. The heaviest concentration appeared just outside the macular reflex ring. In the retinal periphery of the right eye, in the 9:00 o'clock meridian, was a disk-sized area of depigmentation. No glial or pigmentary clumping was noted in association with the latter. Two such depigmented areas were noted in the temporal periphery of the retina in the left eye. The choroidal and retinal vasculatures appeared normal. Intraocular tension appeared normal on palpation. Confrontation tests showed normal fields. Color vision was normal (Ishihara test).

3-10.—Mrs. R. D., a well developed woman aged 45, had no specific ocular complaints. She denied having night blindness. Uncorrected visual acuity was 6/6 —2 in the right eye and 6/6 —3 in the left eye. External ocular examination showed a normal condition except for minor lateral deviation under cover. The pupillary reflexes were normal. Funduscopic examination revealed no pathologic changes except for the presence of occasional opacities in the vitreous of each eye. The disks were normal in size and color, and the retinal vasculature was normal. An excellent foveal reflex was seen in the macular area of each fundus. Retinal pigment was normal and of only moderate amount. Appearing in and about the macular area were a myriad of small yellow, glistening deposits, which were deep to the retinal vessels. Their density decreased as one approached the retinal periphery. The left fundus is illustrated in figure 2B; the picture in the right eye was very similar. Although the central portions of the fundi presented a golden, glittering appearance as seen with the ophthalmoscope, the reflex from the fundus appeared normal in intensity and hue when viewed from a distance in a darkened room.

The visual fields appeared normal in the confrontation test. Palpation revealed normal intraocular tension bilaterally. Color vision was normal (Ishihara).

3-11.—Mrs. W. E., aged 41, who was without children, was studied by Dr. Raymond C. Warner, of Milwaukee. On the basis of his report, we unhesitatingly classify her as a fifth heterozygous female in sibship 3.

"There was no history of ocular injury or inflammation and no ocular complaints other than a slight blurring of vision for a short time after awakening in the morning. There was no night blindness. The patient had never worn glasses. The irides appeared normal and were blue. External ocular examination showed nothing significant. Examination with the slit lamp disclosed a faint discoid shadow in the posterior pole of the left lens, but no classification was possible. The central media and lenses were otherwise clear.

"On dilation, the pupils were round and equal. Funduscopic examination of the right eye revealed an irregular, round disk, with very high central branching. There was venous pulsation in the cup, which was funnel shaped, with a deep physiologic depression. The lamina cribrosa was faintly seen. Rings of pigment were present, with an increase in the pigmentation temporally. The retinal arteries and veins appeared somewhat smaller than average, but the ratio was 4:5. The entire macular area presented a glistening, golden, wartlike appearance. The foveal reflex was present. These golden granules were confined almost entirely to the macular area, with little evidence of their existence toward the periphery. The left fundus was very similar to the right, but the central gold, glittering, granular change in the macular area was more pronounced than in the right eye and somewhat more extensive in its distribution. One gained the impression of ripples of golden sand distributed over a reddish background. No peripheral lesions were seen in either fundus.

"Intraocular tension was normal to touch in both eyes. Visual acuity without correction was 6/6 —2 in the right eye and 6/6 —1 in the left eye. Retinoscopic study showed a correction of +1.50 sph.  $\subset$  +0.50 cyl., axis 110 in the right eye and of +1.50 sph.  $\subset$  +0.25 cyl., axis 110 in the left eye. Corrected vision was 6/6 in the right eye and 6/6 —1 in the left eye."

With a 5/330 test object, the visual fields showed only minor peripheral constriction in the left eye. Measurements of muscle function were within normal limits.

6-1.—Mrs. N. R., aged 34, asthenic and moderately dark-complexioned, occasionally experienced asthenopic symptoms in association with close ocular work but denied having night blindness or progressive visual failure. Uncorrected visual acuity was 6/9 —2 in the right eye and 6/30 in the left eye, correctable to 6/6 in each eye. The results of external ocular examination were without significance except for a moderate overshoot of the left eye when she was looking up and to the right. The near point of convergence was 115 mm., and there was considerable lateral deviation under cover. The central media, disks and vessels were normal in both eyes: A glistening, golden granular reflex was present throughout the retina and extended almost to the extreme periphery. A few patches of retinal depigmentation, measuring from  $\frac{1}{8}$  to  $\frac{1}{4}$  disk diameter, were noted in the extreme nasal and temporal peripheries of each fundus. These patches were oval or round. No specific clumping of pigment could be seen. Intraocular tension was normal to palpation, and the fields were normal as tested by confrontation. Color vision was normal (Ishihara).

8-2.—Mrs. H. Ch., aged 35, had fundi showing the typical tapetal-like reflex and her only child was a boy (25-1) having retinitis pigmentosa. She denied having any ocular symptoms, particularly with respect to night blindness or pro-

gressive loss of vision. Uncorrected visual acuity was 6/9 —1 in the right eye and 6/6 in the left eye. Some facial asymmetry was noted, the left orbit being slightly higher than the right. External ocular examination was without significance except for mild blepharitis marginalis sicca and the presence of slight overshooting of the opposite eye when she was looking up to the right or to the left. The central media were clear, except for a few strandlike opacities in the vitreous. The disks were normal, and a good foveal reflex was seen in each macula. The golden, glistening change was seen throughout the fundus except in the extreme periphery of each eye. In the peripheral areas there were several smaller and some larger areas of moth-eaten retinal atrophy or pigmentary mottling and some rather large verrucae, but no clumping of the bone corpuscle type. The choroidal vessels were vividly seen, and there was no evidence of arteriosclerosis of either the retinal or the choroidal vasculature. The fields were full as tested by confrontation. Color vision was abnormal, as will be described in a later section.

8-4.—N. P., a boy aged 10 years, according to his parents, became completely blind during the last few months of his life and died of convulsions on Nov. 30, 1924. Dr. C. W. Rucker furnished the following information:

"The patient registered at the Mayo Clinic on June 12, 1924, at the age of 10 years. At that time he had symptoms of a cerebellopontile tumor. Surgical exploration was advised, but permission was refused by the father. There are no follow-up notes on our findings, for the boy was apparently taken home and died there six months later. Ophthalmologic examinations conducted here on June 13 revealed that the pupils and pupillary reflexes were normal. The fields appeared full on a rough test. There were choking of both optic disks and elevation of 3 D. Since such patients are examined with the use of homatropine mydriasis, the examining physician had a good look at the fundus, and to him it appeared normal, with no evidence of retinitis pigmentosa."

Because of the boy's early death, we have chosen to regard the condition of this child as "unknown" and to exclude the case for statistical purposes.

8-5.—Mrs. O. L., aged 31, had the typical golden, granular appearance of the fundi, but she did not complain of any visual difficulty or ocular discomfort. While at first admitting that she had difficulty in seeing at night, she was not definite about this; moreover, she was the only woman who mentioned any difficulty of this kind. The uncorrected vision was 6/4.5 —3 in each eye. The pupillary reflex was normal bilaterally. Extraocular movements were normal except for a definite overshooting of the left eye when she was looking up and to the right, but no hyperphoria was demonstrated with the cover test. Medium-sized medial pingueculae were present bilaterally. The central media were normal. The disks were normal, and a good foveal reflex was seen in each eye. The glittering, golden, verruciform bodies in the choroid or retina appeared to be more concentrated about the disks and macular areas in this patient than in other affected women. There were some pigmentary washing and faded mottling (depigmentation) in the periphery of each eye, and a disk-sized area of atrophy was noted in the periphery of the left fundus at 3:00 o'clock. No glial changes or perivascularitis was observed. The choroidal and retinal vessels were normal. With the confrontation test the fields seemed normal. The same form of anomalous color vision found in 8-2 was present in this patient.

9-1.—O. R. H., a man aged 29, was reported to have severe visual difficulty, but examination revealed no signs of the choroidoretinal disease under investigation. According to Dr. E. S. Schmidt, the patient had had purulent conjunctivitis of both eyes, which was treated at the age of 4 weeks, with residual corneal opacification. Our examination in 1946 showed right hypertropia. The eyes

were straight in the primary position, and there was horizontal nystagmus with occasional vertical and rotatory components. The cover test also showed a lateral right divergent strabismus of approximately 15 degrees. The right cornea showed a macular scar of 4 mm., which encroached on the visual axis from below, and a similar scar was present in the left cornea, but was nebulous. An anterior polar cataract was present in the right eye, the lens of the left eye being clear. The fundi were normal except for situs inversus vasorum in each eye. Uncorrected vision was 1/60 in the right eye and 6/21 in the left eye, and the patient wore correction for an extensive hyperopic astigmatism. Color vision was normal (Ishihara). The maternal grandfather was said to have had poor vision and nystagmus.

11-2.—Mrs. G. D. W., aged 26, disclaimed having symptoms suggestive of night blindness and had no ocular complaints. Uncorrected visual acuity was 6/6 —4 in the right eye and 6/6 +3 in the left eye. The cover test disclosed definite convergence, but the eyes were straight in the primary position. The pupillary reflexes were normal. The central media were clear except for a few strandlike opacities in the vitreous of the left eye. There was an excellent foveal reflex in the macular area of each fundus. The golden, tapetal-like reflex was present in both retinas, mostly concentrated in and about the disk and macular area and thinning out toward the periphery. There was some moth-eaten mottling of the pigment in the periphery of each eye. Intraocular tension was normal on palpation. Confrontation tests revealed normal fields. Color vision was normal (Ishihara).

22-2.—N. D. R., a boy aged 12, of slender build, had had mumps and erysipelas at the age of 1 year. At about this time the parents also were aware that the child was extremely near-sighted. He complained of night blindness after starting to school, at the age of 6 years. Examination at the age of 4 years by A. N. Abbott, D.O., revealed a "peppery fundus" in each eye, and vision was recorded as 10/200 for both eyes. Retinoscopic examination indicated a correction of —6.75 sph.  $\ominus$  —1.75 cyl., axis 15 for the right eye and —7.00 sph.  $\ominus$  —2.00 cyl., axis 160 for the left eye at this time.

External examination performed in the home at the age of 12 years revealed a mild but definite head tremor. The eyes were straight in the primary position. The ocular excursions showed overactivity of the inferior oblique muscle when he was looking up to the right or to the left. There were considerable divergence under cover and moderate nystagmoid jerking in the extremes of gaze. The pupillary reflexes were normal. Fundusoscopic examination showed many small, strandlike opacities of the vitreous. The disks were of good color and possessed normal capillarity. A small temporal myopic conus was seen in each eye. The macular areas showed no foveal reflexes, and there was distinct clumping of pigment granules scattered in and about the macular region. The retinal vessels were slightly smaller than normal. Nasal to the disk, both superiorly and inferiorly, the retina was distinctly atrophic, with numerous pinpoint flecks and larger aggregations of pigment. The choroidal vasculature was vividly seen but seemed to be deficient throughout, possibly as a result of the myopia. Large vortex veins were observed in the superior and inferior nasal periphery. Migratory pigment had outlined a few of the smaller peripheral vessels of the retina. The superior temporal portion of the retina was likewise atrophic, but here the pigment clumping assumed the more typical bone corpuscular, or lattice-like, pattern. A few scattered, dull gray verrucae were seen in the extreme periphery. The inferior temporal portion of the periphery was less atrophic but likewise showed unmistakable evidence of degeneration. The fundi were quite similar in appearance, but the pathologic process seemed to be more advanced in the right eye. In the con-



frontation test the fields showed extreme contraction. With a  $-8.00$  sphere for the right eye and a  $-9.00$  sphere for the left, corrected vision was 6/12  $-1$  and 6/15  $+1$ , respectively. Color vision was normal (Ishihara).

25-1.—J. Ch., a blond, slender boy aged 13, had noticed a visual handicap, which seemed to be getting severer and was more apparent at dusk. His teacher had requested an ocular examination when he was only 7 years of age. Through the courtesy of A. N. Abbott, D.O., we learned that in September 1945 the refractive error was  $+2.00$  sph.  $\ominus -3.00$  cyl., axis 180 in each eye and that the corrected visual acuity was 20/20 in each eye. With the same correction, vision in July 1947 was 20/30 in the right eye and 20/25 in the left eye.

Our examination in September 1946 (at the age of 13) revealed a grossly normal external condition. The irides were blue, with much gold and brown around the pupillary margin. The central media were normal. The optic nerve heads were normal except for slight pallor. The macular areas were devoid of any pathologic condition, but no foveal reflex could be seen in either eye. The retinal vasculature was normal. The retinas were atrophic in the superior temporal and nasal quadrants, the pigmentary clumping assuming a linear, strandlike, interdigitating network rather than the usual bone corpuscle appearance. This retinal change encroached on the macular zone from above, and similar changes appeared in the periphery nasally and inferiorly, but were here much more remote from the central area. The temporal portion of the retina seemed to be wholly intact. The choroidal vessels were most vividly seen in the atrophic zones of the retina and did not show evidence of sclerosis. These changes were remarkably symmetric in the two eyes. Confrontation tests of the fields showed minor peripheral constriction, which was more marked superiorly in both eyes, despite the fundic picture. Color vision was normal.

31-1.—B. E. W., a 6 year old, slightly obese girl, had a visual acuity of 6/15 in each eye with the Snellen E chart. We were told that she had no visual difficulties and was doing well in school. External examination showed slight ptosis of the left lid and a minimal, but definite, epicanthus in each eye. The eyes were straight in the primary position, and there was minor esophoria under cover. The remainder of the external examination was noncontributory. Fundusoscopic study showed a nearly complete pigment ring about the optic disk in each retina. The optic nerve heads and the retinal vessels were normal. There were numerous glistening, yellow, verruciform deposits about the disks and macular areas. These deposits were present elsewhere throughout the fundus but were less numerous in the periphery. The fundi of this girl showed less pigment than did those of the other affected women studied, and the choroidal vasculature was vividly seen. No other pathologic changes were noted. The fields were normal in the confrontation test. Color vision was normal on the Ishihara line charts.

32-1.—J. L. P., a well developed 4 year old girl, had uncorrected visual acuity of approximately 6/15 in each eye with the Snellen E chart. The child had no specific ocular complaints, and the parents denied that there was evidence of night blindness. External ocular examination revealed no pathologic condition. The fundusoscopic examination also showed a normal condition except for the presence of yellow, glistening verrucae scattered throughout the entire fundus except in the central macular areas. As in most children of this age, the peripheral retinal pigment was somewhat sparse. This girl showed less manifestation of the tapetal-like reflex of the fundus than did any of the other female patients. Retinoscopic examination, performed with paredrine and atropine cycloplegia, gave the following correction: right eye:  $+1.25$  sph.  $\ominus 0.0$ ; left eye:  $+1.25$  sph.  $\ominus +0.37$  cyl., axis 178. Color vision was not tested.

32-2.—J. E. P., a somewhat anemic-appearing girl, aged  $2\frac{1}{2}$  years, was first seen on Sept. 8, 1947. The parents stated that she started to walk later than normal and was continually falling over objects and bumping into furniture. It was impossible to determine the degree of visual acuity, but it was evidently poor. The eyes were straight in the primary position, but there was marked lateral deviation under cover, which at times was sufficiently pronounced to be considered an incipient divergent strabismus. Fundusoscopic examination showed a few vitreous opacities in each eye. The disks were large and oval horizontally and of normal color and capillarity. A small inferior temporal retinal conus was present in each eye. The fundi were those of a blonde person, with the associated myopic changes. The choroidal circulation was prominent, and the vasculature seemed sparse. There was a conspicuous paucity of retinal pigment, but no abnormality was seen. An extensive distribution of minute, glistening gold bodies was seen extending from the macula to the periphery in each fundus. At first these were difficult to see, owing to the poorly developed pigmentary background in these fundi. Refraction with paredrine and atropine cycloplegia revealed the following errors: right eye:  $-9.50$  sph.  $\subset -0.25$  cyl., axis 5; left eye:  $-9.50$  sph.  $\subset -2.00$  cyl., axis 180. With this correction, the child was reported to be getting about the house with less difficulty. Fields were difficult to determine by confrontation, but we were unable to detect any specific defects. Color vision was not tested.

#### MODE OF INHERITANCE

The distribution of cases of retinitis pigmentosa and tapetal reflex in the pedigree (fig. 1) obviously suggests the presence of a sex-linked gene producing both abnormalities. The affected males are in all cases sons of mothers having the tapetal trait. On the assumption of a sex-linked factor which produces retinitis pigmentosa in males and the tapetum-like fundus in heterozygous females, we should expect equal numbers of affected and normal children among both sons and daughters of women showing the tapetal trait. Among children of affected males, however, all daughters, but no sons, would be expected to be affected. The observed frequencies found by pooling the children of such families (table 1) are in obvious agreement with these expectations. The propositus (12-1) and his mother (3-9) are omitted in tallying the children of sibships 12 and 3, since these sibships were ascertained through these affected members. Sibship 3 is listed separately, since the mother is not actually known to have possessed the tapetum-like fundi.

In the last two columns of table 1, the total numbers of sons and daughters are compared, such totals including unexamined as well as examined children. Among the children of affected females, the ratio of sons to daughters is 12:18, a deviation in the direction expected if prenatal death occurred in some of the males inheriting the pathologic gene. However, the deviation is not statistically significant, nor does the ratio of 3 normal sons to 3 affected sons among the children examined tend to support the assumption of reduced viability of affected males.

As with all pedigrees suggesting sex linkage, one must consider an alternative genetic hypothesis, namely, that of an autosomal gene pro-

ducing different phenotypes in the two sexes. According to this hypothesis, affected males would produce affected sons and normal daughters with a total probability equal to that for normal sons and affected daughters. In the two sibships supplying information on this point, namely, 6 and 32, there occurred no affected sons or normal daughters among 5 children examined. The probability of this event is  $\frac{1}{32}$ , a figure which constitutes significant evidence against the hypothesis of autosomal inheritance.

One may also consider the possibility of a partially sex-linked gene<sup>4</sup> having different manifestations in the two sexes. The father (1-2) of sibship 3 had a history of progressive blindness, and, although the few available facts do not suggest the presence of the disease found in his descendants, he may for the moment be considered to have been affected. His children would then best be explained by assuming him to be heterozygous for a partially sex-linked gene, the abnormal gene being

TABLE 1.—*Frequencies of Normal and Affected Children of Affected Males and Females*

Children of:	Affected Sons	Normal Sons	Affected Daughters	Normal Daughters	Total Sons	Total Daughters
2-3 (presumably affected female).	1	1	4*	1	4	8
Affected females...	2†	2	4	6	8	10
Affected males.....	0	2	3	0	4	4

\* The mother of the propositus, 3-9, is omitted.

† The propositus, 12-1, is omitted.

on the paired portion of his x-chromosome. One would then have to count 3-1 and 3-2 as representing cross-overs and the remaining 6 examined children non-cross-overs. However, having crossed over to the y-chromosome, the gene in 3-2 would now be expected to pass preferentially to sons; hence, the data on sibship 6 would require the postulation of 3 cross-overs, an improbable result. Ordinary sex-linkage, with the gene located in the unpaired portion of the x-chromosome, appears to be a much more probable explanation.

The fact that the sex-linked gene producing retinitis pigmentosa in this family is incompletely recessive, i. e., produces an observable effect in heterozygotes, is not unusual. Levit<sup>5</sup> found this to be true of the majority of human sex-linked abnormalities known in 1936, and additional examples have since been reported.<sup>6</sup> Red-green color blindness

4. Haldane, J. B. S.: A Search for Incomplete Sex-Linkage in Man, *Ann. Eugenics* **7**:28-57, 1936.

5. Levit, S. G.: The Problem of Dominance in Man, *J. Genet.* **33**:411-434, 1936.

6. Rundles, R. W., and Malls, H. F.: Hereditary (? Sex-Linked) Anemia, *Am. J. Med. Sc.* **211**:641-58, 1946. Gates, R. R.: *Human Genetics*, New York, The Macmillan Company, 1946, p. 1518.

and hereditary optic atrophy are examples of sex-linked ocular anomalies which are frequently manifested in heterozygous women. Choroide-remia has recently been shown to belong to this group and will be discussed more fully later. Still other ocular anomalies showing this mode of inheritance have been studied at the Heredity Clinic and will be reported in subsequent articles.

## COLOR VISION

All persons examined in this study, with the exception of young children, were tested for defects in color vision by means of Ishihara plates. Such tests seemed particularly desirable in the study of this kindred, since the commoner forms of "color blindness" are sex linked and the opportunity to investigate the cross-over frequency between

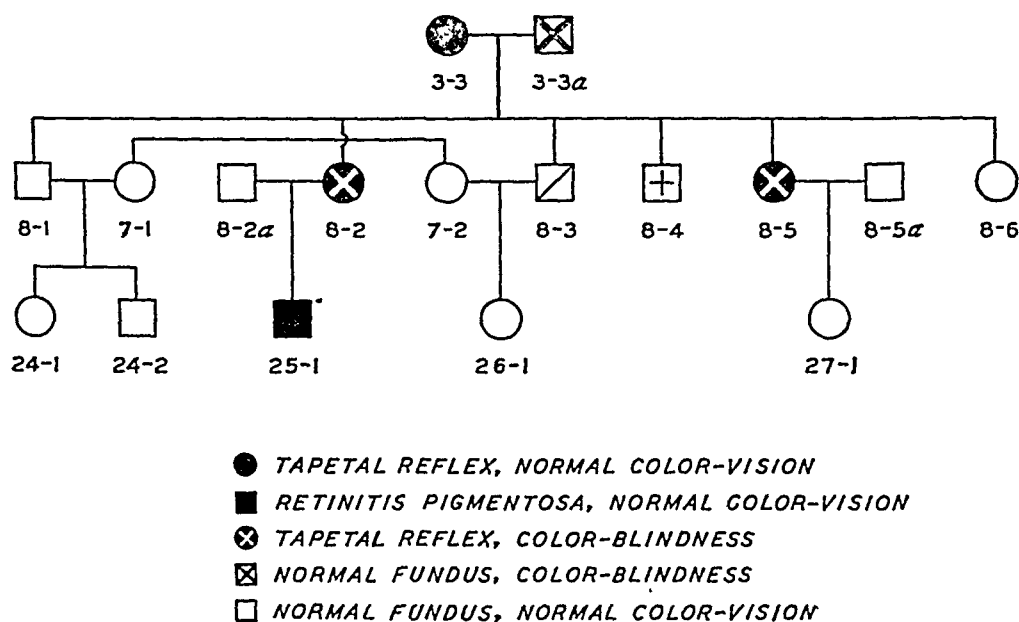


Fig. 3.—Pedigree chart showing color blindness in 2 sisters with tapetal-like reflex and their color-blind father.

retinitis pigmentosa and color blindness might therefore be presented. Of 30 males and 34 females tested, only 3 cases of defective color vision were encountered, but these happened to be strategically situated and of unusual interest. The cases were those of 2 sisters with the tapetum-like fundi, 8-2 and 8-5, and their color blind father, 3-3a (fig. 3). The anomaly, in so far as can be judged from the Ishihara test, was very similar in these 3 subjects, but the responses differed from those which are characteristic of deuteranopia or deuteranomaly (table 2).

Assuming that the gene responsible for this form of color blindness is sex linked, it is evident that 8-2 and 8-5 are only heterozygous for it, since 8-2 has produced a son with normal color vision. Moreover, to be homozygous, 8-2 and 8-5 would have had to receive the factor from 3-3, an event rendered improbable by the

absence of color blindness among her many collateral relatives. Now, occasional defective color vision in heterozygous females is not unusual. But the question then arises why the third daughter of 3-3a, namely 8-6, being likewise, by hypothesis, heterozygous, is not color blind. The fact that she alone of the 3 daughters failed to inherit the tapetum-like fundus suggests that a form of interaction of these two genes may have produced color blindness in her sisters. Chance association cannot, however, be excluded.

Since 8-2 and 8-5 have inherited the two abnormal genes on different x-chromosomes, we may count 25-1 as representing a non-cross-over, since he possesses retinitis pigmentosa without color blindness. The daughter of 8-5 failed to inherit the tapetal character and has also

TABLE 2.—*Test Responses to Color Vision Plates\**

Ob- server	Sex	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
3-3	♀	12	8	6	29	57	5	3	15	24	2	6	97	45	5	7	16	23	..	..	..	..	26	42	35	96
3-3a	♂	12	..	..	..	27	..	8	15	74	..	6	..	..	..	7	16	..	..	..	..	..	2	4	3	9
8-1	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
8-2	♀	12	3	6	20	..	2	3	17	21	..	..	..	..	..	..	..	..	..	..	..	..	2	4	3	9
8-5	♀	12	8	6	20	33	2	5	13	21	..	6	..	..	..	9	..	..	..	..	..	..	2	4	3	9
8-6	♀	12	8	6	29	57	5	8	15	71	2	6	87	45	9	7	16	23	..	..	..	..	26	42	35	96
7-1	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
24-1	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
24-2	♂	12	8	6	29	57	5	8	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
8-2a	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
25-1	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
7-2	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
26-1	♀	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
8-5a	♂	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96
27-1	♀	Normal on plates 26, 27, 28 and 32																								

\* The plates in the Ishihara "Tests for Colour-Blindness," seventh edition (Tokyo, Kanehara, 1936).

normal color vision; but, in view of the variation shown by 8-2, 8-5 and 8-6, we cannot definitely conclude that 27-1 lacks the gene for color blindness, and we must therefore consider her indeterminate with respect to crossing over.

#### COMMENT

Retinitis pigmentosa is well known for its diversity of clinical manifestations, and, as might therefore be expected, the genetics of this disease suggests that it may result from many different genotypes. In addition to (1) autosomal recessive inheritance, which appears to account for the majority of cases, there have been described numerous pedigrees showing (2) dominant autosomal inheritance and a few showing (3) sex-linked recessive inheritance. Furthermore, Haldane<sup>4</sup> has shown that some of the pedigrees formerly attributed to autosomal dominant or recessive genes are more probably due to genes located in the paired portions of the x- and y-chromosomes. We may thus

add (4) dominant partial sex linkage and (5) recessive partial sex linkage to the possible modes of inheritance of retinitis pigmentosa. In addition, retinitis pigmentosa is observed in at least two well known genetic syndromes, namely, the syndrome of Laurence-Moon-Bardet-Biedl (retinitis pigmentosa, polydactyly, obesity and hypogenitalism) and the juvenile form of amaurotic idiocy. Finally, there are a number of allied abiotrophies of the retina and choroid which sometimes show their relation to retinitis pigmentosa by replacing or antedating the latter condition in a given patient or by occurring in other members of the same kindred. Included in the latter group are retinitis pigmentosa sine pigmento, retinitis punctata albescens, atrophía gyrata choroideae et retinae, choroideremia and night blindness.

Of particular interest to the present discussion are the sex-linked forms of choroidoretinal degeneration. Pedigrees of sex-linked retinitis pigmentosa are scarce. In her extensive (1922) compilation of 297 published family histories, Bell<sup>7</sup> presented but one pedigree with definite indication of sex linkage, this being a kindred studied by Nettleship and later investigated more extensively by Usher.<sup>8</sup> All members examined by Usher were males who exhibited myopia of 2 to 8 D.; heterozygous women regularly showed myopia without retinitis pigmentosa. Additional pedigrees of sex-linked retinitis pigmentosa have been described by Gasalla,<sup>9</sup> Seggel,<sup>10</sup> Frazer,<sup>10</sup> McQuarrie<sup>11</sup> and Allan.<sup>12</sup> None of these authors reported fundusoscopic changes in any female members of their families. This raises the question whether the kindred described in this paper differs in this respect from other pedigrees of the sex-linked trait, or whether previous authors have merely failed to note the minor fundusoscopic changes in heterozygous women.

Another possibility is that the disease in the present family is actually an example of one of the several variants of retinitis pigmentosa. Choroideremia (so-called) is of particular interest in this respect, for several reasons. It has been found to occur almost exclusively in

7. Bell, J.: *Retinitis Pigmentosa and Allied Diseases*, in *Treasury of Human Inheritance* (Galton Laboratory, University of London), 1922, vol. 2, plates i-xxvi, pp. 1-123.

8. Usher, C. H.: *On a Few Hereditary Eye Affections*, Tr. Ophth. Soc. United Kingdom **55**:164-245, 1935.

9. Gasalla, M. L.: *L'hérédité dans une famille atteinte de rétinite pigmentaire*, Bull. et mém. Soc. franç. d'opht. **44**:169-73, 1931.

10. Seggel and Frazer, cited by Usher.<sup>8</sup>

11. McQuarrie, M. D.: *Two Pedigrees of Hereditary Blindness in Man*, J. Genet. **30**:147-53, 1935.

12. Allan, W.: *Eugenic Significance of Retinitis Pigmentosa*, Arch. Ophth. **18**:938-947 (Dec.) 1939.

males. Mauthner,<sup>13</sup> Koenig<sup>14</sup> and Wolf<sup>15</sup> each described the condition in brothers. More extensive genetic studies by Smith and Usher,<sup>16</sup> Zorn,<sup>17</sup> Schutzbach,<sup>18</sup> Goedblad<sup>19</sup> and Waardenburg<sup>20</sup> have shown the disease to be sex linked. Goedblad, in particular, emphasized the fact that heterozygous females regularly show a "salt and pepper" appearance of the fundus. McCullough and McCullough<sup>21</sup> recently confirmed this mode of inheritance in two large American families. Heterozygous females are described as having a combination of pigmentative and depigmentative changes in the fundi, occurring chiefly in the midperiphery. Small, irregular or squarish accumulations of pigment are interspersed with pale or yellowish areas of depigmentation, which radiate in irregular bands toward the ora serrata. This abnormality of the fundus was invariably present in genetically ascertained carriers. It appeared to be constant with age and was unaccompanied with any detectable changes in vision.

Niccol<sup>3</sup> described a brother and sister with large oval defects of the choroid at the macula in each eye, unaccompanied with mental defect or skeletal changes. The parents were unrelated, but in the mother's eyes the maculas were "stippled with light yellow specks like gold dust, lying deeper than the retinal vessels and not definitely related to them in distribution—what appears to be an example of tapetal reflex."

Gyrate atrophy of the choroid and retina is another condition resembling retinitis pigmentosa, and it has been reported to occur in families which also contain cases of retinitis pigmentosa or choroideremia. Waardenburg<sup>22</sup> described a sex-linked recessive pedigree of gyrate

13. Mauthner, L.: Ein Fall von Choroideremie, Ber. d. Naturw.-med. Verein in Innsbruck **2**:191-197, 1871-1872.

14. Koenig, H.: Zwei Beobachtungen von mangelhafter Entwicklung der Choroidea verbunden mit Hemeralopie, Inaug. Dissert., Griefswald, 1874.

15. Wolf, S.: Choroideremia, Arch. Ophth. **3**:80-87 (Jan.) 1930.

16. Smith, H. E., and Usher, C. H.: Choroideremia and Two Other Varieties of Night Blindness in the Same Pedigree, Roy. London Ophth. Hosp. Rep. **26**:157-174, 1916.

17. Zorn, B.: Ueber familiäre atypische Pigmentdegeneration der Netzhaut (totale Aderhautatrophie), Arch. f. Ophth. **101**:1-13, 1920.

18. Schutzbach, M.: Ueber erbliche Aderhaut-Netzhauterkrankung, Arch. f. Ophth. **138**:315-331, 1938.

19. Goedblad, J.: Mode of Inheritance of Choroideremia, Ophthalmologica **194**:308-315, 1942.

20. Waardenburg, P. J.: Choroideremie als Erbmerkmal, Acta ophth. **20**:235-274, 1942.

21. McCullough, C., and McCullough, R. J. P.: A Hereditary and Clinical Study of Choroideremia, Tr. Am. Acad. Ophth. **52**:160-190, 1948.

22. Waardenburg, P. J.: Das menschliche Auge und seine Erbanlagen, The Hague, Nijhoff, 1932.

atrophy but did not mention any fundusoscopic peculiarities of heterozygotes.

On the basis of the aforementioned facts, some authors have suggested that retinitis pigmentosa, choroideremia, gyrate atrophy and congenital night blindness are all stages of the same disease process. Inasmuch as sex-linked inheritance has been observed in certain cases of all these diseases, a unitarian concept would perhaps seem more attractive if restricted to the sex-linked forms of choroidoretinal degeneration. However, even here the available facts are too few to warrant the assumption of a single sex-linked gene or a common mode of pathogenesis. With regard to the present family, a definite classification of the pathologic changes is impossible. At present, the fundus picture in the 3 males examined most closely resembled retinitis pigmentosa, but it is quite possible that the picture of "choroideremia" might supervene at a later date. That the present disease may be somewhat distinct, however, is perhaps best suggested by the fundusoscopic appearances in carrier females. In three large kindreds showing sex-linked choroidoretinal degeneration, we have observed distinct differences in the abnormalities in the fundi of heterozygous women. In one family, the males show fundi typical of "choroideremia," and heterozygous females show minor pigmentative changes, like those described by Schutzbach and the McCulloughs. In a second family—the present one—the fundi of males are more typical of retinitis pigmentosa, while those of females show the golden granular change which we have described as a "tapetal reflex." In a third family, males, again, have fairly typical retinitis pigmentosa or retinitis punctata albescens, but none of the heterozygotes show detectable abnormalities of the fundus. In view of the uniformity within kindreds, we feel that the variations are probably not due to modifying genes acting on the same sex-linked gene, but that different sex-linked genes are probably present in these families. They could, of course, be allelic mutations, and they might also have very similar mechanisms of pathogenesis.

#### SIGNIFICANCE OF THE TAPETUM-LIKE FUNDUS

Observing the abnormal fundi of the 2 women originally seen in this study, one of us (H. F. F.) was led to describe the anomaly as a "tapetal reflex," since the picture reminded him of the cases described by Mann.<sup>1</sup> It is possible that this appearance is identical with or similar to that described in carriers of "choroideremia." However, having made the analogy with a tapetum, we were led to further comparisons in the literature, which it may be of interest to relate here. Mann observed that the fundi of her 2 women most nearly resembled the patchy golden fundus of the galago, a nocturnal lemuroid primate. This is interesting, since it is known<sup>23</sup> that a tapetum lucidum is found

23. Walls, G. L.: *The Vertebrate Eye*, Bloomfield Hills, Mich., Cranbrook Press, 1942.



among primates only in night monkeys of the genus *Aotus* and in two lemuroid genera, *Galago* and *Loris*. Regarding the two latter, Johnson<sup>24</sup> wrote in 1901:

I have noticed in certain night animals, more particularly in the *Galagos* and *Lorides*, a heaping-up of pigment all around the periphery, which, seen with the ophthalmoscope, greatly resembles *Retinitis pigmentosa*. Exposing a *Galago* to daylight for some months, I found it to go quite blind; the invasion of the pigment could clearly be seen to advance concentrically towards the posterior pole, as I have seen the disease spread in Man . . . I thought that these observations on night animals pointed to the possibility of arresting the insidious progress of the disease, of which blindness is the invariable termination, by shielding the eyes from the most active rays of daylight. A few attempts to do this by the use of spectrum-blue goggles . . . have given encouraging results, and I am therefore persevering in that direction.

Similar observations on *galagos* have been made by Hardy,<sup>25</sup> and it is interesting that Dr. Johnson's analogy is now reenforced by the knowledge that at least one form of *retinitis pigmentosa* in man has a heterozygous manifestation which simulates the fundus of a normal *galago*. The possibility that some forms of primary retinal degeneration may be dependent on an abnormal photochemical reaction of the neuro-epithelium has been suggested by others. Leber<sup>26</sup> proposed this view and called attention to the fact that other hereditary diseases are known in which the action of an abnormal gene is evidently potentiated by light, e. g., *xeroderma pigmentosum* and *congenital porphyrinuria*. Embryologic studies by Bourne and others (cf. Grüneberg<sup>27</sup>) in a strain of rat possessing an inherited pigmentary degeneration of the retina have shown that retinal development is apparently normal up to the time the eyes open, whereupon degenerative changes almost immediately set in.

In citing the foregoing references, it is our purpose only to call attention to an etiologic theory which would seem to merit further investigation. Regarding the pathologic significance of the tapetal-like change in the fundus seen in the present family, little can be said except that we are inclined to regard this abnormality as a forerunner of a more extensive change in the choroid or retina, which leads to retinal degeneration in males. According to this view, one would perhaps expect to observe the abnormality at an early age in males, but no opportunity to investigate this point was offered in this study, since

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24. Johnson, G. L.: *Contributions to the Comparative Anatomy of the Mammalian Eye, Chiefly Based on Ophthalmoscopic Examination* [plates 1-30], Phil. Tr. Roy. Soc. London, s. B **194**:1-82, 1901.

25. Hardy, L.: Personal communication to the authors, 1947.

26. Leber, T.: *Die Krankheiten der Netzhaut*, in Graefe, A., and Saemisch, T.: *Handbuch der gesamten Augenheilkunde*, Berlin, Julius Springer, 1916, vol. 7, pt. 2, p. 1222.

27. Grüneberg, H.: *Animal Genetics and Medicine*, New York, Paul B. Hoeber, Inc., 1947.

none of the heterozygous women had sons younger than 10 years of age. At the ages of 12, 13 and 30 years, none of the affected males in this family showed the golden granular change in any portion of the fundus. In families with choroideremia, the typical female fundus was found in young males by the McCulloughs.<sup>21</sup> These authors suggested that the heterozygous change in the fundus in persons with choroideremia is probably a stationary anomaly. There is some suggestion in our family that the abnormality may be a slowly progressive one in females, but much more careful study would be needed to establish this. Whereas the McCulloughs asserted that the areas of depigmentation in the fundi of carriers of choroideremia are probably due to thinning of the choroid and visualization of the sclera, we have interpreted the golden granules seen in the carriers in our family as evidence of hyperplastic change, perhaps, as suggested by Mann,<sup>1</sup> thickenings or verrucae in the lamina vitrea (lamina basalis).

The practical significance of the tapetum-like fundus is apparent. By the presence or absence of this anomaly one may distinguish, in a family possessing sex-linked retinitis pigmentosa, those females capable of transmitting the disease from those who are not. Thus, in the present family, those females (*viz.*, 3-3, 3-8, 3-10, 3-11, 8-5, 11-2, 31-1, 32-1 and 32-2) who exhibit the tapetal-like reflex but have not yet produced children, or, having children, have not yet produced sons with retinitis pigmentosa, have been warned concerning this possibility. On the other hand, those females who but for the absence of this fundic picture might also have been suspected of being carriers (*viz.*, 8-6, 11-3, 13-1, 13-2, 22-1, 27-1 and numerous descendants of 3-1) can be assured that they have little or no chance of producing blind sons.

The practicing ophthalmologist will seldom be able to examine a large number of relatives of his patients. However, on the basis of this study and other recent reports, it would seem definitely advisable for him to examine carefully all the close relatives of patients having retinitis pigmentosa or related conditions, even though all these relatives are reported to have good visual acuity. If, for example, a male patient with retinitis pigmentosa has what appears to be a negative family history for the disease, one might suspect that the responsible genetic factor is an autosomal recessive. However, the finding of a tapetum-like fundus or similar abnormality in this patient's mother, or in a sister or daughter, would strongly suggest the presence of a sex-linked form of choroidoretinal degeneration. This would considerably alter one's predictions concerning the likelihood of defective children and grandchildren. Further study of the carriers of such sex-linked genes by clinical, biochemical and, when possible, histologic methods would also undoubtedly add greatly to our understanding of this important group of diseases.

## A METHOD OF PRESERVATION OF ANIMAL EYES

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BY PRACTICE on animal eyes interns and residents in ophthalmology acquire skill, familiarity, confidence and courage in handling their instruments and in executing the standard surgical maneuvers. Large numbers of animal eyes are needed for the teaching and examination of these students and for investigational use in ophthalmic surgery. In some states their use is discountenanced, and it is difficult or impossible to obtain them, especially on short notice. At best, it may be difficult to procure them in sufficient quantity when wanted, because of lack of material and of men who can remove them without damage. Hence there arose the idea of finding a method of preservation so that a large number of eyes could be on hand when and where needed.

The eyes of kittens 6 to 8 weeks old are quite satisfactory if enucleated shortly after death. In most large cities they can be obtained with little trouble from societies for prevention of cruelty to animals.

The enucleation must be carefully performed. With Stevens' tenotomy scissors the lids are dissected completely away from their attachment to the orbital margin and the canthal ligaments. The conjunctiva is then grasped as close to the orbital wall as possible, and the dissection is carried out by slight traction on the globe and by keeping the scissors close to the orbital wall to avoid cutting the sclera. This technic permits removal of the muscles and the deep retrobulbar tissues with their attachments to the eyeball intact. These appendages are wanted for clamping the eye when it is used. The optic nerve is severed as far back as possible.

Chemical methods of preservation were tried but were rejected because they toughen the coats of the eye and cloud the cornea. Freezing the eyes in isotonic solution gives much better results. Quick freezing with the lids *in situ*, that is with the cornea covered and protected, was first tried, but after five or six days the eyes became unsuitable for cataract extraction and operations for glaucoma because release of the ocular pigment into the anterior chamber made it difficult or impossible to see any details. The corneas were only slightly cloudy at first but became more so if the eyes were handled the least bit roughly.

The method of preservation found most successful and now recommended is immersion and freezing of the eyes in an ice cube tray filled with Locke's solution. To keep the cornea pointed upward and approximately in the middle of the compartment, a small lead weight is attached to the appendages at the back of the globe. With Locke's solution the cornea remains clear. The eyes are frozen at a temperature of 10 F. in an ordinary refrigerator. The freezing process takes approximately one hour. No difference was found in the state of preservation of the eyes whether they were frozen rapidly or slowly. After the cubes are thoroughly frozen they can be kept for any length of time at a temperature slightly below freezing. The advantage of preserving the eye in the middle of an ice cube is that no special care need be taken in the handling, as the jacket of ice protects the eye from any trauma. When one or more eyes are required, it is necessary only to run cool water on the tray and as many cubes as desired can be removed, the rest being replaced for use later. The cool water is run on the cube until the cornea is just free from ice. The water is then run on the posterior portion of the cube until the ice jacket can be removed without causing damage. Water should not be run on the posterior portion of the cube until it is completely thawed inside, since the frozen posterior portion aids in fixing the eyes in the operating mask or other device. To suit convenience, the entire contents of the tray may be removed at one time, and the individual cubes, separated by strips of wax paper, may be replaced in the refrigerator or stored in a "deep freeze" unit at 10 F. After removal of the ice jacket, the eye becomes soft enough for use in about ten minutes when kept at room temperature.

If the eye should be too soft, clamping of the muscle cone close to the globe will readily raise the tension. The anterior chamber can be deepened as desired if a solution of fresh gelatin is introduced into it at the limbus by means of an ordinary hypodermic syringe and needle; but if care is taken in defrosting the posterior portion of the globe, this procedure is usually unnecessary. A rotary movement of the needle facilitates its entry into the chamber.

For transportation, the ice cubes containing the eyes may be packed between sheets of dry ice<sup>®</sup> (carbon dioxide snow) 1 inch (2.5 cm.) in thickness in an insulated cardboard box. Insulated cardboard boxes may be obtained from any ice cream company or any company handling dry ice.<sup>®</sup> The boxes are sealed with tape. A 1 inch linear opening is left in the top of the box to allow for the escape of carbon dioxide. If this opening were not made, the box would rupture from the accumulation of carbon dioxide. So packed, the eyes will remain frozen while in transit for three days.

## SUMMARY

A method is presented of preserving and transporting animal eyes for use in the practice of ophthalmic surgery. The eyes are weighted individually with a lead bob to keep them in position and are frozen in Locke's solution as ice cubes in an ordinary refrigerator. For shipment the eyes are packed in dry ice.

NOTE.—The eyes prepared as described in this paper were used in the laboratory and found to be satisfactory by the late Dr. T. L. Terry, of Boston, and by Dr. D. B. Kirby, of New York.

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## INDEX TO VOLUME 40

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The asterisk (\*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

- Abnormalities and Deformities:** See under names of organs and regions, as Extra-pyramidal Tract; Eyes; etc.
- Abscess:** See under names of organs and regions
- Accommodation and Refraction:** See also Glasses; etc.  
 clinical aniseikonia, \*326  
 combined red filter and occluder with several uses, 100  
 dissatisfied refraction patient, 97  
 "duction test"; evaluation of various technics, 90  
 effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285
- Acetylcholine:** See Choline and Choline Derivatives
- Achromatopsia:** See Color Blindness
- Acid, Ascorbic:** See Ascorbic Acid  
 Cevitamic: See Ascorbic Acid
- Acridine Dyes;** deep keratitis associated with atypical lichen planus; report of case, \*138
- Acrolynia, infantile, photophobia associated with,** 356
- Adler, F. H.:** Localizing value of visual fields in patients with early chiasmal lesions, \*579
- Adrenal Preparations;** practical application of denervated iris, \*317
- Aiken, S. D.:** Ocular changes in acute disseminated lupus erythematosus, 86
- Air, preplacement in cyclodialysis,** \*134
- Albright, F.:** Hypercalcemia and band keratopathy; report of 19 cases, \*624
- Alcohol, Wood:** See Methyl Alcohol
- Allen, J. H.:** Evisceration with intrascleral implant; new technic, 98  
 Treatment of staphylococcal corneal ulcerations with antitoxin, 80
- Allergy:** See Anaphylaxis and Allergy
- Amaurosis:** See Blindness
- Amblyopia:** See Blindness
- Anaphylaxis and Allergy;** ocular allergy, 221  
 studies in experimental ocular tuberculosis; effect of streptomycin and "promizole" on experimental ocular tuberculosis in immune-allergic rabbit, \*413
- Anesthesia;** ocular allergy [cocaine], 221  
 practical application of denervated iris, \*317
- Anesthetics:** See Anesthesia
- Angioid Streaks:** See under Retina
- Angioma of choroid,** 363
- Angioscotoma:** See Scotoma
- Angiospasm:** See under Retina
- Animals;** electrophoretic patterns of concentrated aqueous humor of rabbit, cattle and horse, \*279  
 method of preservation of animal eyes, \*704
- Aniseikonia:** See Accommodation and Refraction
- Anisometropia:** See Accommodation and Refraction
- Anomalies:** See under names of organs and regions, as Eyes; etc.
- Anophthalmos:** See Eyes, absence
- Anopsia:** See Blindness
- Antisepsis and Antiseptics;** experimental and clinical study of antiseptic action of merbromin ("mercurochrome"), 367
- Antitoxin Therapy:** See Cornea
- Apparatus:** See also Instruments  
 fixation light, \*351
- Aqueous Humor;** chemical natures in glaucomas, 84  
 cholinesterase in aqueous of eye, \*273  
 electrophoretic patterns of concentrated aqueous humor of rabbit, cattle and horse, \*279
- Arachnodactyly, clinical course of ocular complications of,** \*558  
 Marfan's syndrome associated with ectopia lentis, 221
- Archiv für Ophthalmologie, Albrecht von Graefe's,** 77
- Area Martegiani:** See Vitreous Humor
- Armed Forces Personnel:** See Military Medicine; etc.
- Arteries:** See also Blood pressure; Blood vessels; Thrombosis; etc.  
 cilioretinal, occlusion of, \*152  
 hyaloid, persistence of, 219  
 Hypertension: See Blood pressure, high  
 Retinal: See Retina, blood supply
- Arthritis:** See also Reiter's Disease
- Ascorbic Acid;** chemical natures of aqueous humor in glaucoma, 84
- Atabrine:** See Acridine Dyes
- Atkinson, W. S.:** Delayed keratitis due to mustard gas (dichlorodiethyl sulfide burns); report of 2 cases, \*291  
 Mercury in lens (hydrargyrosis lentis), 79
- Atopy:** See Anaphylaxis and Allergy
- Atrophy:** See under names of organs and regions, as Iris; Nerves, optic; etc.
- Atropine;** effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285

- Atropine—Continued  
sulfate; practical application of surface-active drugs in ophthalmology, \*675
- Austin, G.: Localizing value of visual fields in patients with early chiasmal lesions, \*579
- Autokeratoplasty: See Cornea, ulcer
- Avitaminosis: See under Vitamins; and under names of deficiency diseases
- Bacilli: See Bacteria
- Bacteria: See also Meningococci; Staphylococci; Typhoid; etc.  
Calmette-Guérin: See Tuberculosis contaminated ophthalmic ointments, \*39  
experimental investigation of pathogenicity of diphtheroids isolated from human conjunctiva, \*23  
Granulosis: See Trachoma  
new oculobuccal-genital syndrome; report of case with verification of acid-fast bacilli and pathologic examination, 355  
Tularensis: See Tularemia  
Typhoid Group: See Typhoid
- Bair, D.: Vision in strabismus; preliminary report, \*438
- Barbital and Barbitol Derivatives; minimal retinal arterial hypotension in fatal barbiturate intoxications, 362
- Barbiturates: See Barbitol and Barbitol Derivatives
- Barkan, H.: Evaluation of methods and results of cataract operations as performed in private and clinic practice at Stanford University Hospitals, 79
- Barkan, O.: Operation for congenital cataract, \*680
- Bartter, F. C.: Hypercalcemia and band keratopathy; report of 19 cases, \*624
- Bedell, A. J.: Diagnosis of retinoblastoma, \*311  
Keratitis due to Cephalosporium, 79  
Ophthalmoscopy and operations for reduction of high blood pressure, \*483
- Benton, C. D., Jr.: Treatment of ocular syphilis with penicillin, \*302
- Berke, R. N.: Tenotomy of superior oblique muscle for hypertropia, 99
- Birth, Premature: See Premature Infants
- Blepharitis: See Eyelids
- Blepharoplasty: See under Eyelids
- Blindness: See also Vision; etc.  
alterations of visual fields in tobacco amblyopia, 368  
Color: See Color Blindness  
modifications of critical fusion frequency in course of tobacco amblyopia, 234  
of 42 years' duration; cure by keratoplasty, 220  
vision in strabismus; preliminary report, \*438
- Blindspot: See Retina
- Bloch, F. J.: Retinal tumor associated with neurofibromatosis (von Recklinghausen's disease); report of case, \*433
- Blood, calcium; hypercalcemia and band keratopathy; report of 19 cases, \*624  
Circulation: See Arteries; etc.
- Blood—Continued  
fats and lipoids; lipemia retinalis associated with essential hyperlipemia, \*570  
fats and lipoids; lipemia retinalis; report of case, 88  
modifications of formula of blood in thrombosis of central retinal vein, 361  
pressure, high; fundus in cases of hypertension in which Smithwick method was used, 222  
pressure, high; nonperforating thermometric cyclodiathermy in treatment of hypertensive uveitis, \*509  
pressure, high, ophthalmoscopy and operations for reduction of, \*483  
pressure, low; minimal retinal arterial hypotension in fatal barbiturate intoxications, 362  
proteins; cholinesterase in aqueous of eye, \*273  
proteins; electrophoretic patterns of concentrated aqueous humor of rabbit, cattle and horse, \*279  
transfusion, spontaneous profuse hemorrhage from conjunctiva of both eyes in infant treated with, 353  
Vessels: See also Arteries; etc.  
vessels; use of roentgen therapy for retinal diseases characterized by new-formed blood vessels (Eales's disease; retinitis proliferans); preliminary report, \*389
- Blue Haloes: See Vision
- Bodian, M.: Aid in detecting trachoma-like inclusion bodies in conjunctiva, \*147
- Bones: See under names of bones
- BOOK REVIEWS:  
Abramson, H. A.: Psychodynamics and Allergic Patients, 370  
Bailey, P.: Intracranial Tumors, 237  
Bulletin of Ophthalmological Society of Egypt, 238  
Burki, E.: Haftglas, 577  
Children's Eye Nursing; J. H. Daggart, 479  
Collected Reprints from Wilmer Ophthalmological Institute of Johns Hopkins University and Hospital, 481  
Cowan, A.: Refraction of Eye, 481  
Daggart, J. H.: Children's Eye Nursing, 479  
Haftglas; E. Burki, 577  
Intracranial Tumors; P. Bailey, 237  
Krimsky, E.: Management of Binocular Imbalance, 369  
Larmande, A. M.: Neuro-angiomatose encephalo-faciale, 369  
Management of Binocular Imbalance; E. Krimsky, 369  
Neuro-angiomatose encephalo-faciale; A. M. Larmande, 369  
Neurosurgical Pathology; I. M. Scheinker, 577  
Psychodynamics and the Allergic Patient; H. A. Abramson, 370  
Refraction of Eye; A. Cowan, 481  
Scheinker, I. M.: Neurosurgical Pathology, 577  
Short History of Ophthalmology; A. Sorsby, 237  
Sorsby, A.: Short History of Ophthalmology, 237  
Transactions of Ophthalmological Society of Australia (British Medical Association), 479  
W. H. Ross Foundation (Scotland) for Study of Prevention of Blindness, 481

- Bowman Membrane: See under Cornea
- Brain; central visual field after occipital lobectomy, 226  
cerebral complications (papilledema) in epidemic parotitis, 356  
Diseases: See also Mental Diseases  
diseases of brain and optic nerve; concentric restriction of vision from unilateral cerebral lesions, 226  
extensive symmetrical cerebral calcification and chorioretinitis in identical twins (toxoplasmosis?), 222  
localizing value of visual fields in patients with early chiasmal lesions, \*579  
mesencephalic Parinaud's paralysis, 359  
role of diencephalon in regulating ocular tension, 228
- Brambel, C. E.: Dicumarol and rutin in treatment of retinal vascular disorders, 89
- Brown, A. L.: Healing of corneal wounds; variations in adhesive power of fibrin in vitro studies, 80
- Brown, C. P.: Practical application of surface-active drugs in ophthalmology, \*668
- Buffers; cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612  
cornea; swelling properties of fibrous tunic of eye, \*601
- Burian, H. M.: History of Dartmouth Eye Institute, \*163
- Burky, E. L.: Studies in experimental ocular tuberculosis; effect of "promin" and "promizole" in experimental ocular tuberculosis in normal rabbit, \*1
- Burns; delayed keratitis due to mustard gas (dichlorodithyl sulfide burns); report of 2 cases, \*291
- Butler, J. V. B.: Simple operation for entropion, \*665
- Cachexia; types and variants of epibulbar epitheliomas; typical invading and cachexia-producing epithelioma and barely malignant epithelioma arising from keratoconjunctiva (tyloma), 363
- Calcification: See also under Brain; etc.  
occurrence in eye tissues, 222
- Calcium in Blood: See Blood, calcium
- Camera: See Photography
- Canal of Schlemm: See Eyes
- Cancer: See also Chorionepithelioma; Choroid; Epithelioma; Sarcoma; Tumors; and under names of organs and regions, as Eyelids; etc.
- Cardiovascular System: See Arteries; Heart; etc.
- Caruncle: See Lacrimal Organs
- Cataract after tetany, 225  
cancer of eyelid treated by radiation, with consideration of irradiation cataract, 230  
complicating glaucoma, 78  
congenital, operation for, \*680  
congenital, types of, 219  
evaluation of methods and results of operations as performed in private and clinic practice at Stanford University Hospitals, 79  
simple appositional suture for use in operations for, \*347
- Catarrh: See Conjunctivitis, vernal; etc.
- Catgut: See Cataract; Sutures; etc.
- Cattle: See Animals
- Cauterization: See under names of various organs and diseases, as Retina; etc.
- Cells: See also Tissue  
granular cell myoblastoma of orbit, \*14  
Inclusion: See Trachoma
- Cephalosporosis: See Mycosis
- Cerebrospinal Fever: See Meningitis
- Cerebrospinal Fluid, substitution for vitreous clouded with opacities, 365
- Cerebrum: See Brain
- Chandler, B. F.: Cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612  
Cornea; swelling properties of fibrous tunic of eye, \*601
- Chemotherapy: See under names of diseases and chemotherapeutic agents, as Conjunctivitis; Cornea, ulcers; Eyes, diseases; Penicillin; Sulfonamides; Trachoma; etc.
- Chiasm, Optic: See Optic Chiasm
- Children: See also Infants  
primary meningococcal ophthalmia, 219  
xerophthalmia and keratomalacia in, 220
- Chloroethyl Sulfide: See Dichloroethyl Sulfide
- Choked Disk: See Neuritis, optic
- Choline and Choline Derivatives; use of choline in ophthalmology, 233
- Cholinesterase in aqueous of eye, \*273
- Chorionepithelioma; choroid metastases in chorionepithelioma (chorionic carcinoma) of testicle, 231
- Chorioretinitis: See Retinochoroiditis
- Choroid, angioma of, 363  
choroidoretinal degeneration; sex-linked form in which heterozygous women exhibit tapetal-like retinal reflex, \*685  
frequency of secondary carcinomas in, 231  
metastases in chorionepithelioma (chorionic carcinoma) of testicle, 231  
Inflammation: See also Retinochoroiditis  
inflammation; persistence of hyaloid artery, 219  
necrosis of, \*116  
necrosis of malignant melanoma of choroid causing necroses of preexisting tissues, \*113
- Choroiditis: See Choroid, inflammation
- Cilia: See Eyelashes
- Ciliary Body: See Uvea  
Processes: See Uvea  
Region: See Uvea
- Clinics: See also Hospitals; etc.  
evaluation of methods and results of cataract operations as performed in private and clinic practice at Stanford University Hospitals, 79  
oculist in Switzerland, 221
- Clower, J. W.: Clinical experiments with new ways of influencing intraocular tension; effect of rice diet, \*46
- Cocaine: See Anesthesia
- Cogan, D. G.: Hypercalcemia and band keratopathy; report of 19 cases, \*624



- Color Blindness; incidence of defective color vision among psychotic patients, \*121
- Communicable Diseases: See Immunity; Meningitis; Syphilis; etc.
- Comroe, J. H., Jr.: Effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285
- Congress: See Societies
- Conjunctiva, aid in detecting trachoma-like inclusion bodies in, \*147
- calcification; hypercalcemia and band keratopathy; report of 19 cases, \*624
- Catarrh: See Conjunctivitis, vernal
- experimental investigation of pathogenicity of diphtheroids isolated from human conjunctiva, \*23
- local penicillin therapy of hypopyon formation, with reference to use of subconjunctival injection, 232
- ocular changes associated with scrub typhus; study of 451 patients, \*245
- pigmentation of palpebral conjunctiva resulting from mascara, 82
- recession of limbal conjunctiva, 218
- reticulum cell sarcoma of plica semilunaris, 364
- spontaneous profuse hemorrhage from conjunctiva of both eyes in infant treated with blood transfusion, 353
- Xerosis: See Xerophthalmia
- Conjunctivitis: See also Keratoconjunctivitis; Ophthalmia; Reiter's Disease
- Granular: See Trachoma
- Pannus: See Trachoma
- primary meningococcal ophthalmia, 219
- "silent" dacryocystitis, \*157
- vernal, association with conical cornea, \*467
- Contusions: See Cataract; Eyes, injuries; etc.
- Convergence: See Phorias; Strabismus
- Cordes, F. C.: Ocular changes in acute disseminated lupus erythematosus, 86
- Cornea, conical, associated with vernal conjunctivitis, \*467
- conical, and mongolism, \*454
- factors affecting transmission of visible light by fibrous tunic of eye, \*612
- healing of corneal wounds; variations in adhesive power of fibrin in in vitro studies, 80
- histologic study of experimental transplantation, 221
- hypercalcemia and band keratopathy; report of 19 cases, \*624
- infection due to herpes simplex; experimental study, \*531
- Inflammation: See Keratitis; Keratoconjunctivitis
- occurrence of calcification in eye tissues, 222
- lattice type of hereditary degeneration; report of 5 cases, including 1 of child of 2 years, \*189
- Pannus: See Trachoma
- Surgery: See also Cataract; Glaucoma
- surgery; cure of blindness of 42 years' duration by keratoplasty, 220
- surgery; simple appositional suture for use in operations for cataract, \*347
- swelling properties of fibrous tunic of eye, \*601
- Cornea—Continued
- transplantation; surgical technic in rabbits, 354
- ulcers; keratitis due to *Cephalosporium*, 79
- ulcers; local penicillin therapy of hypopyon formation, with reference to use of subconjunctival injection, 232
- ulcers; treatment of staphylococcal corneal ulcerations with antitoxin, 80
- value of corneal peeling or corneal resection in ophthalmology, 81
- xerophthalmia and keratomalacia in children, 220
- Cosmetics; pigmentation of palpebral conjunctiva resulting from mascara, 82
- Costenbader, F.: Vision in strabismus; preliminary report, \*438
- Cotterman, C. W.: Choroidoretinal degeneration; sex-linked form in which heterozygous women exhibit tapetal-like retinal reflex, \*685
- Cranium; tumors of optic nerves; long survival in 3 cases of intracranial tumor, \*56
- Crystalline Lens: See Lens, Crystalline
- Cyanides; experimental studies on retrobulbar neuritis, 90
- Cyclodialysis: See Glaucoma
- Cyclodiathermy: See Urea
- Cysts: See under names of organs and regions, as Iris; etc.
- Cytology: See Cells
- DFF: See Glaucoma
- Dacryocystitis: See Lacrimal Organs
- Dark Adaptation: See Accommodation and Refraction
- Dartmouth Eye Institute, history of, \*163
- Deformities: See under names of organs and regions
- Deficiency Diseases: See Vitamins; etc.
- DeLong, P.: Practical application of surface-active drugs in ophthalmology, \*668
- Dermoid Cyst: See Tumors, dermoid
- Descemet Membrane: See Cornea
- Detergents; practical application of surface-active drugs in ophthalmology, \*668
- Diathermy: See under names of organs, regions and diseases, as Retina, detachment; Urea; etc.
- Dichloroethyl Sulfide; delayed keratitis due to mustard gas (dichlorodethyl sulfide burns); report of 2 cases, \*291
- Dicumarol: See Retina, blood supply
- Diencephalon: See Brain
- Diet and Dietetics: See also Vitamins
- clinical experiments with new ways of influencing intraocular tension; effect of rice diet, \*46
- Diethylstilbestrol: See Estrogens
- Diffusion: See Osmosis and Permeability
- Digitals, visual disturbances due to, 85
- Di-Isopropyl Fluorophosphate: See Glaucoma
- Diphtheroids: See Bacteria
- Diplegia: See Paralysis

- Diplopia, traumatic, treatment of, 224
- Disk, Choked: See Neuritis, optic
- Optic: See Nerves, optic
- Donnelly, E. J.: Contaminated ophthalmic ointments, \*39
- Drugs; practical application of surface-active drugs in ophthalmology, \*668
- Duction Test: See Vision, tests
- Duke-Elder, W. S.: Ophthalmology during war and in future, 85
- Dunnington, J. H.: Granular cell myoblastoma of orbit, \*14
- Dystrophy: See Cornea
- Eales's Disease: See Vitreous Humor
- Ectoderm; development of ectodermal framework of optic nerve, with reference to glial lamina cribrosa, 78
- Ectopia Lentis: See Lens, Crystalline
- Education; medical assistance at professional level, 96
- Electric Stimulation: See Tension
- Electrocoagulation: See under specific headings, as Glaucoma; Retina, detachment; etc.
- Electrons; electronic flash (gas discharge) tube in photography of anterior segment of eye, \*493
- Electrophoresis: See Blood, proteins
- Electrosurgery: See under specific headings
- Embolism: See Thrombosis
- Embryology; trochlear nerve in human embryo and fetus, 353
- Entropion: See under Eyelids
- Enucleation: See under Eyes; Orbit; etc.
- Epicanthus: See under Eyelids
- Epinephrine: See Adrenal Preparations
- Episcleritis: See Sclera
- Epithelioma, epibulbar, types and variants of; typical invading and cachexia-producing epithelioma and barely malignant epithelioma arising from keratoconjunctiva (tyloma), 363
- treatment of epitheliomas of lids with radiation (radium and roentgen rays), 358
- Epithelium: See Cornea; Lens, Crystalline
- Eserine: See Glaucoma
- Esophoria: See Phorias; Strabismus
- Esotropia: See also Strabismus
- blindspot syndrome, \*371
- Estrogens; phlyctenular keratoconjunctivitis in young girl in relation to menstrual cycle, 220
- Eucatropine Hydrochloride; practical application of surface-active drugs in ophthalmology, \*674
- Evisceration: See under Eyes
- Exophoria: See Strabismus
- Exophthalmos, noninflammatory, 228
- progressive, 361
- relative; measurement by roentgenography, 225
- Extrapyramidal Tract; divergence excess; anomaly of extrapyramidal system, 358
- Eyelashes; congenital vertical shortness of lids combined with tetrastichiasis, 219
- Eyelids: See also Conjunctiva; Conjunctivitis
- adherent; operative technic for posterior symblepharon, 353
- cancer treated by radiation, with consideration of irradiation cataract, 230
- congenital vertical shortness of lids combined with tetrastichiasis, 219
- lymphosarcoma of; report of case, with death in 40 days, \*518
- ocular changes associated with scrub typhus; study of 451 patients, \*245
- pigmentation of palpebral conjunctiva resulting from mascara, 82
- present evaluation of merits of Z-plastic operation, 360
- simple operation for entropion, \*665
- treatment of epitheliomas of lids with radiation (radium and roentgen rays), 358
- Eyes: See also Orbit; Vision; and under names of special structures and diseases
- Abnormalities: See under names of special structures of eye
- absence; esthetic correction of unilateral anophthalmos by ophthalmoprostheses, \*497
- Accommodation: See Accommodation and Refraction
- Anesthesia: See Anesthesia
- Anomalies: See under names of special structures of eye and diseases
- Blood Supply: See Retina, blood supply
- changes associated with scrub typhus; study of 451 patients, \*245
- changes in acute disseminated lupus erythematosus, 86
- clinical course of ocular complications of arachnodactyly, \*558
- cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612
- cornea; swelling properties of fibrous tunic of eye, \*601
- Cysts: See under names of special structures of eye
- Diseases: See also Glaucoma; Ophthalmia; Trachoma; Xerophthalmia; etc.
- diseases; experimental and clinical study of antiseptic action of merbromin ("mercurochrome"), 367
- diseases; penicillin in ophthalmology, 367
- diseases; sodium sulfacetimide, 366
- diseases; vitamin P in ophthalmology, 367
- electronic flash (gas discharge) tube in photography of anterior segment of, \*493
- Enucleation: See Eyes, surgery
- evisceration with intrascleral implant; new technic, 98
- Examination: See also Accommodation and Refraction; Foreign Bodies; Vision, tests; etc.
- examination; fixation light, \*351
- examination; nearly 100 years of ophthalmoscope, \*268
- hemorrhage; use of vitamin K in treatment of intraocular hemorrhages, 368
- Humors: See Aqueous Humor; Tension; Vitreous Humor
- Injuries: See also under Cataract; etc.
- injuries; necrosis caused by trauma, \*111
- method of preservation of animal eyes, \*704

## Eyes—Continued

Movements: See also Paralysis; Strabismus; etc.  
 movements; mesencephalic Parinaud's paralysis, 359  
 Muscles: See Muscles; Orthoptics; Paralysis; Phorias; Strabismus  
 necrosis of intraocular tissues, \*101  
 new oculobuccal-genital syndrome; report of case with verification of acid-fast bacilli and pathologic examination, 355  
 occurrence of calcification in eye tissues, 222  
 ocular allergy, 221  
 Paralysis: See Paralysis  
 Pigmentation: See Retinitis pigmentosa; and under special structures of eyes  
 primary and secondary changes in tularemia, 354  
 Proptosis: See Exophthalmos  
 Refraction: See Accommodation and Refraction  
 surgery; method of preservation of animal eyes, \*704  
 surgery; use of thrombin-gelatin sponges in ophthalmic surgery, 228  
 Tension: See Glaucoma; Tension  
 Tuberculosis: See Tuberculosis  
 use of dead tissue in ophthalmic repair, 227

Face, malignant reticular tumors of, 231

Falls, H. F.: Choroidoretinal degeneration; sex-linked form in which heterozygous women exhibit tapetal-like retinal reflex, \*685

Feeble-mindedness: See Idiocy

Feer's Disease: See Acrodynia

Feldman, J. B.: Practical application of surface-active drugs in ophthalmology, \*668

Felix-Weil Reaction: See Trachoma

Festschrift for Joseph Meller, 574

Fetus; trochlear nerve in human embryo and fetus, 353

Fever: See Typhoid; etc.  
 Japanese River: See Tsutsugamushi Disease

Fibrin; healing of corneal wounds; variations in adhesive power of fibrin in in vitro studies, 80

Fingers and Toes, Abnormalities: See Arachnodactyly

Fink, W. H.: "Duction test"; evaluation of various techniques, 90

Fistula, congenital, of lacrimal sac, 358

Flavones; vitamin P in ophthalmology, 367

Food: See Diet and Dietetics; Vitamins

Foramen Hyaloidae: See Vitreous Humor

Fovea Centralis: See Macula Lutea

Foxglove: See Digitalis

Frost, Albert D., Memorial Library, 77

Fundus Oculi: See under Retina

Furmethide: See Glaucoma

Galvanism: See Tension

Ganglion, cells; pathogenesis of laesio ganglii vesiculi optici, 234

Gelatin; use of thrombin-gelatin sponges in ophthalmic surgery, 228

Genetics: See Glaucoma

Genitals, new oculobuccal-genital syndrome; report of case with verification of acid-fast bacilli and pathologic examination, 255

Gillette, D. F.: Visual disturbances due to digitalis, 85

Glasses: See also Accommodation and Refraction

clinical anisokonia, \*326

Glaucoma: See also Tension

acute; follow-up study, 223

cataract complicating, 78

chemical natures of aqueous humor in, 84  
 di-isopropyl fluorophosphate (DFP) in treatment; further observations, \*176

early, diagnosis of, 82

effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine of human eye, \*285

hemorrhagic, peripupillary web of vessels in, 357

indications for iridectomy in hemicyclodialysis, 223

medical versus surgical treatment of, \*332

preplacement of air in cyclodialysis, \*134  
 role of diencephalon in regulating ocular tension, 228

role of heredity in, 357

use of choline in ophthalmology, 233

use of furmethide in comparison with pilocarpine and eserine for treatment of, 357

Goiter: See Exophthalmos

Goldsmith, J.: Deep keratitis associated with atypical lichen planus; report of case, \*138

Gonioscopy: See Eyes, examination; Glaucoma

Graduate Work: See Education

von Graefe, Albrecht; Archiv für Ophthalmologie, 77

Grafts: See under Cornea; Eyelids; etc.

Grant, F. C.: Localizing value of visual fields in patients with early chiasmal lesions, \*579

Grant, H. W.: Diagnosis of early glaucoma, 82

Grant, W. M.: Electronic flash (gas discharge) tube in photography of anterior segment of eye, \*493

Granuloma; influence of hypersensitivity on endogenous uveal disease, 232

Grönblad-Strandberg Syndrome: See Pseudoxanthoma elasticum; Retina, blood supply

Grossmann, E. E.: Lipemia retinalis associated with essential hyperlipemia, \*570

Guyton, J. S.: Use of roentgen therapy for retinal diseases characterized by new-formed blood vessels (Eales's disease; retinitis proliferans); preliminary report, \*389

Haden, H. C.: Development of ectodermal framework of optic nerve, with reference to glial lamina cribrosa, 78

Halberstädter-Prowazek Inclusion Bodies: See Trachoma

- Hardy, L. H.: Incidence of defective color vision among psychotic patients, \*121
- Hart, W. H.: Cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612
- Cornea; swelling properties of fibrous tunic of eye, \*601
- Hawk, P. P.: Esthetic correction of unilateral anophthalmos by ophthalmoprostheses, \*497
- Hay Fever: See Anaphylaxis and Allergy
- Head, injuries; treatment of traumatic diplopia, 224
- Heart; visual disturbances due to digitalis, 85
- Heath, P.: Medical assistance at professional level, 96
- Hematology: See Blood
- Hemicyclodialysis: See Glaucoma
- Hemorrhage: See under Conjunctiva; Eyes; Glaucoma; Retina; etc.
- Heredity: See Glaucoma
- Herpes of iris, \*112
- simplex, infection of cornea due to; experimental study, \*531
- Heterophoria: See Phorias; Strabismus
- Heterotropia: See Strabismus
- Heyman, A.: Treatment of ocular syphilis with penicillin, \*302
- Hitz, J. B.: Lipemia retinalis associated with essential hyperlipemia, \*570
- Holt, L. B.: Clinical experiments with new ways of influencing intraocular tension; effect of rice diet, \*46
- Homatropine hydrobromide; practical application of surface-active drugs in ophthalmology, \*674
- Hormones: See Adrenal Preparations; Estrogens; etc.
- Horrax, G.: Tumors of optic nerves; long survival in 3 cases of intracranial tumor, \*56
- Horse: See Animals
- Hospitals; evaluation of methods and results of cataract operations as performed in private and clinic practice at Stanford University Hospitals, 79
- New York as ophthalmological center, 223
- Hughes, W. L.: Combined red filter and occluder with several uses, 100
- Hyaloid Canal: See under Vitreous Humor
- Hydrargyrosis Lentis: See Lens, Crystalline
- Hydrogen Ion Concentration: See also Tissue
- cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612
- cornea; swelling properties of fibrous tunic of eye, \*601
- Hypercalcemia: See Blood, calcium
- Hyperergy: See Anaphylaxis and Allergy
- Hyperlipemia: See Blood, fats and lipoids
- Hypertension: See Blood pressure, high
- Ocular: See Tension
- Hypertonia: See Tension
- Hypertropia, tenotomy of superior oblique muscle for, 99
- Hypheemia: See Eyes, hemorrhage
- Hypopyon: See Cornea, ulcers
- Hypotension: See Blood pressure, low
- Hypotony: See Tension
- Idiocy, mongolian; conical cornea and mongolism, \*454
- Illumination: See Lighting
- Imbecility: See Idiocy
- Immunity: See also Anaphylaxis and Allergy; etc.
- studies in experimental ocular tuberculosis; effect of streptomycin and "promizole" on experimental ocular tuberculosis in immune-allergic rabbit, \*413
- Inclusion Bodies: See Trachoma
- Infants: See also Children
- Premature: See Premature Infants
- spontaneous profuse hemorrhage from conjunctiva of both eyes in infant treated with blood transfusion, 353
- Inflammation, Corneal: See Keratitis
- Ocular: See Ophthalmia; and under special structures of eyes
- Injuries: See Trauma; and under names of organs and regions, as Eyes; Head; etc.
- Instruments: See also Apparatus
- combined red filter and occluder with several uses, 100
- for use in recession operation for squint, 100
- nearly 100 years of ophthalmoscope, \*268
- Intraocular Tension: See Glaucoma; Tension
- Ions: See Hydrogen Ion Concentration
- Iridectomy: See Glaucoma
- Iris: See also Pupils
- denervated, practical application of, \*317
- herpes of, \*112
- inflammation; treatment of iritis with penicillin, \*305
- necrosis, \*117
- necrosis caused by circulatory disturbance (iridodialysis), \*102
- spontaneous cyst of, 231
- Iritis: See Iris, inflammation
- Ishihara Test: See Color Blindness
- Jaffe, N. S.: Cholinesterase in aqueous of eye, \*273
- Practical application of denervated iris, \*317
- Japanese River Fever: See Tsutsugamushi Disease
- Jensen's Disease: See Retinochoroiditis
- Journals: See Periodicals
- Keratotomy: See under Cornea
- Keratitis: See also Keratoconjunctivitis
- deep, associated with atypical lichen planus; report of case, \*138
- delayed, due to mustard gas (dichlorodimethyl sulfide burns); report of 2 cases, \*291
- due to Cephalosporium, 79
- Interstitial: See also Trachoma
- interstitial; treatment with penicillin, \*302
- Trachomatous: See Trachoma

- Keratoconjunctivitis, actinic, 354  
 phlyctenular, in young girl in relation to menstrual cycle, 220  
 types and variants of epibular epitheliomas; typical invading and cachexia-producing epithelioma and barely malignant epithelioma arising from keratoconjunctiva (tyloma), 363
- Keratoconus: See Cornea, conical
- Keratomalacia: See Cornea
- Keratopathy: See under Cornea
- Keratoplasty: See under Cornea
- Kilgore, G. L.: Value of corneal peeling or corneal resection in ophthalmology, 81
- Koch, F. L. P.: Lipemia retinalis; report of case, 88
- Koff, R.: Preplacement of air in cyclo-dialysis, \*134
- Kronfeld, P. C.: Chemical natures of aqueous humor in glaucomas, 84
- Kussmaul-Maier Disease: See Periarteritis nodosa
- Lacrimal Canal: See Lacrimal Organs
- Lacrimal Organs, Fistula: See Fistula  
 lymphangioendothelioma of orbit simulating lacrimal gland, 363  
 massive polyp of lacrimal sac cured without intervention, 358  
 "silent" dacryocystitis, \*157
- Lamina Cribrosa: See Sclera
- Vitreous: See Choroid
- Lectures in ophthalmology, 574
- Lehrfeld, L.: Contaminated ophthalmic ointments, \*39  
 Medical versus surgical treatment of glaucoma, \*332
- Leinfelder, P. J.: Experimental studies on retrobulbar neuritis, 90
- Lens, Crystalline: See also Zonule of Zinn  
 action of sulfanilamide on rabbits' lenses in vitro, 224  
 arachnodactyly (Marfan's syndrome) associated with ectopia lentis, 221  
 clinical course of ocular complications of arachnodactyly, \*558  
 necroses of, \*117  
 necrosis caused by retention of lens matter, \*110  
 Opacity: See Cataract  
 retrolental fibroplasia; preliminary report, \*341
- Leopold, I. H.: Di-isopropyl fluorophosphate (DFP) in treatment of glaucoma; further observations, \*176  
 Effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285
- Levitt, J. M.: Occlusion of cilioretinal artery, \*152
- Libraries; Albert D. Frost Memorial Library, 77
- Lichen planus, atypical, associated with deep keratitis; report of case, \*138
- Light; actinic keratoconjunctivitis, 354  
 Adaptation: See Accommodation and Refraction  
 cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612
- Light—Continued  
 photophobia associated with infantile acrodynia, 356
- Lighting; electronic flash (gas discharge) tube in photography of anterior segment of eye, \*493  
 fixation light, \*351
- Limbus Conjunctivae: See under Conjunctiva
- Cornea: See Cornea
- Lipemia: See Blood, fats and lipoids
- Lipoids in Blood: See Blood, fats and lipoids
- Lloyd, R. I.: Clinical course of ocular complications of arachnodactyly, \*558  
 Pseudotumors of macula, 89
- Lupus erythematosus, acute disseminated, ocular changes in, 86
- Lymphangioendothelioma of orbit simulating lacrimal gland, 363
- Lymphosarcoma of eyelid; report of case, with death in 40 days, \*518
- McDonald, P. R.: Di-isopropyl fluorophosphate (DFP) in treatment of glaucoma; further observations, \*176
- McGraw, J. L.: Infection of cornea due to herpes simplex; experimental study, \*531
- MacLean, A. L.: Dicumaryl and rutin in treatment of retinal vascular disorders, 89  
 Instrument for use in recession operation for squint, 100
- McMackin, J. V.: Fixation light, \*351
- Macule, J. P.: Clinical anisokonia, \*326
- McPhail, A.: Vision in strabismus; preliminary report, \*438
- Macula Lutea: See also Vision  
 hole after single hemorrhage, 229  
 pseudotumors of, 89
- Maier-Kussmaul Disease: See Periarteritis nodosa
- Malformations: See under names of organs and regions
- Marfan's Syndrome: See Arachnodactyly
- Mascara: See Cosmetics
- Medical Societies: See Societies
- Medicine: See Ophthalmology; etc.
- Military: See Military Medicine
- Meibomian Gland: See Eyelids
- Melanoma; necrosis of malignant melanoma of choroid causing necroses of preexisting tissues, \*113
- Meller, Joseph, Festschrift for, 574
- Meningitis: See also Meningococci  
 meningeal reactions in sympathetic ophthalmitis, 365
- Meningococci: See also Meningitis  
 primary meningococcal ophthalmia, 219
- Menstruation; phlyctenular keratoconjunctivitis in young girl in relation to menstrual cycle, 220
- Mental Diseases; incidence of defective color vision among psychotic patients, \*121
- Merbromin: See Mercury
- Mercurochrome: See Mercury

- Mercury; experimental and clinical study of antiseptic action of merbromin ("mercurochrome"), 367  
in lens (hydrargyrosis lentis), 79
- Mesencephalon: See Brain
- Methyl Alcohol; pathogenesis of laesio ganglii vesiculi optici, 234
- Military Medicine; treatment of traumatic diplopia, 224
- Miosis: See Pupils
- Miotics: See Pupils
- Mongolism: See Idiocy, mongolian
- Moore, D. H.: Electrophoretic patterns of concentrated aqueous humor of rabbit, cattle and horse, \*279
- Morphine; effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285
- Mouth; new oculobuccal-genital syndrome; report of case with verification of acid-fast bacilli and pathologic examination, 355
- Movements: See Eyes, movements; Muscles
- Mucous Membranes; new oculobuccal-genital syndrome; report of case with verification of acid-fast bacilli and pathologic examination, 355
- Mumps: See Parotitis
- Murphey, P. J.: Esthetic correction of unilateral anophthalmos by ophthalmoprostheses, \*497
- Muscles, extraocular, surgical treatment of, 93, 227  
Ocular: See Strabismus  
Paralysis: See Paralysis  
tenotomy of superior oblique muscle for hypertropia, 99
- Mustard Gas: See Dichloroethyl Sulfide
- Mycosis; keratitis due to Cephalosporium, 79
- Mydriatics: See Pupils
- Myoblastoma, granular cell, of orbit, \*14
- Nantz, F. A.: Healing of corneal wounds; variations in adhesive power of fibrin in vitro studies, 80
- Narcosis: See Anesthesia
- Nasal Sinuses: See Sinuses, Nasal
- Nasolacrimal Duct: See Lacrimal Organs
- Necrosis of intraocular tissues, \*101
- Needling: See Cataract
- Neoplasms: See Sarcoma; Tumors
- Neostigmine; effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285
- Nerves: See also Neuritis; Paralysis; etc.  
Blocking: See Anesthesia  
optic; blindspot syndrome, \*371  
optic; development of ectodermal framework of optic nerve, with reference to glial lamina cribrosa, 78  
optic; diseases of brain and optic nerve; concentric restriction of vision from unilateral cerebral lesions, 226  
optic; invasion by retinoblastoma, \*553  
optic; lamina cribrosa and its nature, 218  
optic; necrosis of papilla, \*116
- Nerves—Continued  
optic; pathogenesis of laesio ganglii vesiculi optici, 234  
optic; treatment of primary atrophy with penicillin, \*307  
optic, tumors of; long survival in 3 cases of intracranial tumor, \*56  
Paralysis: See under Paralysis  
practical application of denervated iris, \*317  
splanchnic; fundus in cases of hypertension in which Smithwick method was used, 222  
trochlear, in human embryo and fetus, 353
- Nervous System: See Brain; Nerves; etc.
- Neuritis, optic; cerebral complications (papilledema) in epidemic parotitis, 356  
optic; papilledema and papillitis, 229  
optic; retinal hemorrhages preceding papilledema, 229  
optic; treatment of choked disk with penicillin, \*306  
retrobulbar, experimental studies in, 229  
retrobulbar, experimental studies on, 90
- Neurofibromatosis; retinal tumor associated with neurofibromatosis (von Recklinghausen's disease); report of case, \*433
- New York as ophthalmological center, 223
- Newton, F. H.: Esthetic correction of unilateral anophthalmos by ophthalmoprostheses, \*497
- Nicholl, R. J.: Dermoid and epidermoid tumors of orbit, \*639
- Nicotine: See Tobacco
- Nitromersol, aqueous; practical application of surface-active drugs in ophthalmology, \*675
- Nutrition: See Vitamins
- Obituaries:  
Langdon, H. Maxwell, 235
- O'Brien, C. S.: Evisceration with intra-scleral implant; new technic, 98
- Occipital Lobes: See Brain
- O'Connor Clinch Operation: See Strabismus
- Ointments, contaminated ophthalmic, \*39
- Ophthalmia: See also Conjunctivitis; Eyes, diseases; Keratoconjunctivitis  
Egyptian: See Trachoma  
meningeal reactions in sympathetic ophthalmitis, 365  
primary meningococcal, 219  
sympathetic, following subconjunctival rupture of sclera, 366  
sympathetic, new symptom in, 366
- Ophthalmology during war and in future, 85, 223  
history; nearly 100 years of ophthalmoscope, \*268  
history of Dartmouth Eye Institute, \*163  
lectures in, 574  
New York as ophthalmological center, 223  
oculist in Switzerland, 221  
practical application of surface-active drugs in, \*668  
Teaching: See under Education
- Ophthalmoplegia: See Paralysis
- Ophthalmoscope, nearly 100 years of, \*268

- Ophthalmoscopy: See also Eyes, examination; Glaucoma  
and operations for reductions of high blood pressure, \*483
- Ophthalmotonometry: See Tension
- Optic Chiasm; localizing value of visual fields in patients with early chiasmal lesions, \*579
- Optic Disk; Optic Papilla: See Nerves, optic; Neuritis, optic
- Orbit, complications following operations on paranasal sinuses, 361  
dermoid and epidermoid tumors of, \*639  
granular cell myoblastoma of, \*14  
lymphangioendothelioma simulating lacrimal gland, 363  
noninflammatory exophthalmos, 228  
tumors of optic nerves; long survival in 3 cases of intracranial tumor, \*56
- Orthoptics: See also Strabismus  
medical assistance at professional level, 96
- Osmosis and Permeability; cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612  
cornea; swelling properties of fibrous tunic of eye, \*601
- Palsy: See Paralysis
- Pannus: See Trachoma
- Panophthalmitis: See Ophthalmia
- Papilledema: See Neuritis, optic
- Paracentesis: See Eyes, surgery
- Paralysis, mesencephalic Parinaud's paralysis, 359
- Paratrachoma: See Conjunctivitis
- Parietal Lobe: See Brain
- Parotitis, epidemic, cerebral complications (papilledema) in, 356
- Peanut Oil; di-isopropyl fluorophosphate (D F P) in treatment of glaucoma; further observations, \*176
- Penicillin; contaminated ophthalmic ointments, \*39  
Therapy: See Cornea, ulcers; Syphilis; etc.
- Perera, C. A.: Simple appositional suture for use in operations for cataract, \*347
- Periarteritis nodosa, scleral necrosis in, 354
- Perimetry: See Vision
- Periodicals; Albrecht von Graefe's Archiv für Ophthalmologie, 77
- Periphelebitis; successful diathermy treatment of recurring retinal hemorrhage and retinitis proliferans; report of case, \*239
- Perry, I. H.: Experimental investigation of pathogenicity of diphtheroids isolated from human conjunctiva, \*23
- Pfeiffer, R. L.: Dermoid and epidermoid tumors of orbit, \*639
- pH: See Hydrogen Ion Concentration
- Pharynx; new oculobuccal-genital syndrome; report of case with verification of acid-fast bacilli and pathologic examination, 355
- Phlebitis: See Periphelebitis
- Phorias; "duction test"; evaluation of various technics, 90  
tests for heterophoria, 227
- Photography; electronic flash (gas discharge) tube in photography of anterior segment of eye, \*493
- Photophobia: See under Light
- Physostigmine: See Glaucoma
- Pilocarpine: See also Glaucoma  
hydrochloride; practical application of surface active drugs in ophthalmology, \*673
- Plasma: See Blood
- Plastic Surgery; esthetic correction of unilateral anophthalmos by ophthalmoprostheses, \*497  
present evaluation of merits of Z-plastic operation, 360
- Plica Semilunaris: See Conjunctiva
- Poisons and Poisoning: See under names of substances
- Polyp: See Lacrimal Organs
- Posner, M.: Tumors of optic nerves; long survival in 3 cases of intracranial tumor, \*56
- Postgraduate Education: See Education
- Prangen, A. deH.: Surgical treatment of extraocular muscles, 93
- Premature Infants; retrolental fibroplasia; preliminary report, \*341
- Pressure: See Blood, pressure; Tension
- Promin: See Tuberculosis
- Promizole: See Tuberculosis
- Proptosis: See Exophthalmos
- Prosthesis: See under Eyes; Orbit
- Proteins; cholinesterase in aqueous of eye, \*273  
electrophoretic patterns of concentrated aqueous humor of rabbit, cattle and horse, \*279
- Prowazek-Halberstädter Inclusion Bodies: See Trachoma
- Pseudoxanthoma elasticum and angioid streaks, 364
- Pupils, dilatation; di-isopropyl fluorophosphate (D F P) in treatment of glaucoma; further observations, \*176  
dilatation; practical application of denervated iris, \*317  
effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285  
peripupillary web of vessels in hemorrhage glaucoma, 357
- Rabbits: See Animals
- Radiations: See Eyelids; Roentgen Rays; etc.
- Radium Therapy: See under names of various diseases as Eyelids; etc.
- Rados, A.: Conical cornea and mongolism, \*454
- Rand, G.: Incidence of defective color vision among psychotic patients, \*121
- Recklinghausen's Disease: See Neurofibromatosis
- Recruits: See Military Medicine; etc.

- Reese, A. B.: Invasion of optic nerve by retinoblastoma, \*553
- Pigmentation of palpebral conjunctiva resulting from mascara, 82
- Use of roentgen therapy for retinal diseases characterized by new-formed blood vessels (Eales's disease; retinitis proliferans); preliminary report, \*389
- Reflex; choroidoretinal degeneration; sex-linked form in which heterozygous women exhibit tapetal-like retinal reflex, \*685
- Refraction: See Accommodation and Refraction
- Reiter's Disease, 356
- Reticuloendothelial System; malignant reticular tumors of face, 231
- reticulum cell sarcoma of plica semilunaris, 364
- Reticulum: See Reticuloendothelial System
- Retina: See also Macula Lutea
- blindspot syndrome, \*371
- Blood Supply: See also Thrombosis; etc.
- blood supply; angioid streaks, 364
- blood supply; dicumarol and rutin in treatment of retinal vascular disorders, 89
- blood supply; lipemia retinalis; report of case, 88
- choroidoretinal degeneration; sex-linked form in which heterozygous women exhibit tapetal-like retinal reflex, \*685
- detachment; depth of cauterization in surface diathermy, with reference to detachment operations, 362
- detachment; pathogenesis and treatment of detachment of tuberculous origin, 362
- detachment; pseudotumors of macula, 89
- diagnosis of retinoblastoma, \*311
- fundus in cases of hypertension in which Smithwick method was used, 222
- hemorrhage; successful diathermy treatment of recurring retinal hemorrhage and retinitis proliferans; report of case, \*239
- hemorrhages preceding papilledema, 229
- Inflammation: See Retinitis; Retinochoroiditis
- lipemia retinalis associated with essential hyperlipemia, \*570
- migrating ciliary nodules on, 230
- minimal retinal arterial hypotension in fatal barbiturate intoxications, 362
- necrosis of, \*116
- occlusion of cilioretinal artery, \*152
- ocular changes associated with scrub typhus; study of 451 patients, \*245
- ophthalmoscopy and operations for reduction of high blood pressure, \*483
- pathogenesis of laesio ganglii vesiculi optici, 234
- tumor associated with neurofibromatosis (von Recklinghausen's disease); report of case, \*433
- use of roentgen therapy for retinal diseases characterized by new-formed blood vessels (Eales's disease; retinitis proliferans); preliminary report, \*389
- Retinitis; ocular changes in acute disseminated lupus erythematosus, 86
- pigmentosa; choroidoretinal degeneration; sex-linked form in which heterozygous women exhibit tapetal-like retinal reflex, \*685
- Retinitis—Continued
- proliferans, successful diathermy treatment of recurring retinal hemorrhage and retinitis proliferans; report of case, \*239
- use of roentgen therapy for retinal diseases characterized by new-formed blood vessels (Eales's disease; retinitis proliferans); preliminary report, \*389
- Retinoblastoma, diagnosis of, \*311
- in man aged 48 years, 364
- invasion of optic nerve by, \*553
- Retinochoroiditis; extensive symmetrical cerebral calcification and chorioretinitis in identical twins (toxoplasmosis?), 222
- Retinopathy: See under Retina
- Retinoscopy: See under Retina
- Rice; clinical experiments with new ways of influencing intraocular tension; effect of rice diet, \*46
- Rittler, M. C.: Incidence of defective color vision among psychotic patients, \*121
- Robbie, W. A.: Experimental studies on retrobulbar neuritis, 90
- Roentgen Rays; cancer of eyelid treated by radiation, with consideration of irradiation cataract, 230
- Therapy: See under names of organs, regions and diseases, as Eyelids; Retina; etc.
- Roentgenography: See Exophthalmos
- Rome, S.: Preplacement of air in cyclodialysis, \*134
- Runge, P. M.: Method of preservation of animal eyes, \*704
- Rutin: See Retina, blood supply
- Sachs, M.: Nearly 100 years of ophthalmoscopy, \*268
- von Sallman, L.: Electrophoretic patterns of concentrated aqueous humor of rabbit, cattle and horse, \*279
- Mercury in lens (hydrargyrosis lentis), 79
- Samuels, B.: Cataract complicating glaucoma, 78
- Necrosis of intraocular tissues, \*101
- Sarcoma: See also Lymphosarcoma; Tumors; etc.
- reticulum cell sarcoma of plica semilunaris, 364
- Scheie, H. G.: Ocular changes associated with scrub typhus; study of 451 patients, \*245
- Schlemm's Canal: See under Eyes
- Sclera; cornea; factors affecting transmission of visible light by fibrous tunic of eye, \*612
- cornea; swelling properties of fibrous tunic of eye, \*601
- development of ectodermal framework of optic nerve, with reference to glial lamina cribrosa, 78
- evisceration with intrascleral implant; new technic, 98
- lamina cribrosa and its nature, 218
- necrosis, \*115
- necrosis in periarteritis nodosa, 354
- simple appositional suture for use in operations or cataract, \*347
- Surgery: See under Cataract; Glaucoma
- sympathetic ophthalmia following subconjunctival rupture of, 366



- Scopolamine; effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine of human eye, \*285
- Scotoma; alterations of visual fields in tobacco amblyopia, 368  
 blindspot syndrome, \*371  
 diagnosis of early glaucoma, 82  
 new symptom in sympathetic ophthalmia, 366  
 occlusion of cilioretinal artery, \*152
- Scrofula: See Tuberculosis
- Scrub Typhus: See Tsutsugamushi Disease
- Sensitization: See Anaphylaxis and Allergy
- Sex; choroidoretinal degeneration; sex-linked form in which heterozygous women exhibit tapetal-like retinal reflex, \*685
- Shevsky, M. C.: Experimental investigation of pathogenicity of diphtheroids isolated from human conjunctiva, \*23
- Sinuses, Nasal; orbital complication following operations on paranasal sinuses, 361
- Skull: See Cranium
- Smithwick Operation: See Nerves, splanchnic
- Societies; Central Illinois Society of Ophthalmology and Otolaryngology, 574  
 ophthalmological Society of United Kingdom, 77, 574  
 Oregon Academy of Ophthalmology and Otolaryngology, annual meeting, 370
- SOCIETY TRANSACTIONS:  
 American Ophthalmological Society, 78  
 Societe Française d'Ophthalmologie, 575
- Sodium Sulfacetamide: See Eye, diseases
- Soldiers: See Military Medicine
- Spectacles: See Glasses
- Squint: See Strabismus
- Stanford University Hospitals, evaluation of methods and results of cataract operations as performed in private and clinic practice at, 79
- Stansbury, F. C.: Lattice type of hereditary corneal degeneration; report of 5 cases, including 1 of child of 2 years, \*189  
 Lymphosarcoma of eyelid; report of case, with death in 40 days, \*518
- Staphylococci; treatment of staphylococcal corneal ulcerations with antitoxin, 80
- Stell, C.: Esthetic correction of unilateral anophthalmos by ophthalmoprostheses, \*497
- Sterilization; contaminated ophthalmic ointments, \*39
- Stocker, F. W.: Clinical experiments with new ways of influencing intraocular tension; effect of rice diet, \*46
- Strabismus, divergent and concomitant, 359  
 divergence excess; anomaly of extrapyramidal system, 358  
 instrument for use in recession operation for squint, 100  
 orthoptic treatment in convergence insufficiency, 227  
 surgical treatment of extraocular muscles, 93  
 vision in; preliminary report, \*438
- Strandberg-Grönblad Syndrome: See Pseudo-xanthoma elasticum; Retina, blood supply
- Streptomycin, Therapy: See Tuberculosis
- Strong, P. S.: Lipemia retinalis; report of case, 88
- Sulfonamides; action of sulfanilamide on rabbits' lenses in vitro, 224  
 contaminated ophthalmic ointments, \*39  
 Therapy: See Eyes, diseases; etc.
- Sunlight: See Light
- Suprarenal Preparations: See Adrenal Preparations
- Surgery: See Apparatus; Instruments; Sutures; and under names of organs and diseases, as Cataract; Cornea; Eyelids; Eyes; Glaucoma; etc.  
 Plastic: See Plastic Surgery
- Sutures: See also Cataract extraction; etc.  
 simple appositional, for use in operations for cataract, \*347
- Swan, K. C.: Blindspot syndrome, \*371
- Symblepharon: See Eyelids, adherent
- Syphilis, ocular; treatment with penicillin, \*302
- Tapetum Lucidum: See under Choroid
- Tarsectomy: See under Eyelids
- Teaching: See Education
- Technicians: See Orthoptics
- Tenotomy: See Glaucoma
- Tension: See also Glaucoma  
 clinical experiments with new ways of influencing intraocular tension; effect of rice diet, \*46  
 effect of electric stimulation on ocular tension, 361  
 effect of intramuscular administration of morphine, atropine, scopolamine and neostigmine on human eye, \*285  
 role of diencephalon in regulating ocular tension, 228
- Testes; choroid metastases in chorionepithelioma (chorionic carcinoma) of testicle, 231
- Tetany, cataract after, 225
- Tetracaine hydrochloride; practical application of surface-active drugs in ophthalmology, \*673
- Tetrastichiasis: See Eyelashes
- Theodore, F. H.: "Silent" dacryocystitis, \*157
- Thiamine; experimental studies on retrobulbar neuritis, 90
- Thrombin; use of thrombin-gelatin sponges in ophthalmic surgery, 228
- Thrombosis; modifications of formula blood in thrombosis of central retinal vein, 361
- Tissue, intraocular, necrosis of, \*101  
 use of dead tissue in ophthalmic repair, 227
- Tobacco; alterations of visual fields in tobacco amblyopia, 368  
 modifications of critical fusion frequency in course of tobacco amblyopia, 234
- Tonometry: See Tension
- Toxoplasmosis; extensive symmetrical cerebral calcification and chorioretinitis in identical twins (toxoplasmosis?), 222
- Trachoma; aid in detecting trachoma-like inclusion bodies in conjunctiva, \*147  
 recession of limbal conjunctiva, 218

- Transplantation: See under Cornea; etc.
- Trauma; necrosis caused by, \*111  
treatment of traumatic diplopia, 224
- Trephining: See Glaucoma
- Trotter, R. R.: Electronic flash (gas discharge) tube in photography of anterior segment of eye, \*493
- Tsutsugamushi Disease; ocular changes associated with scrub typhus; study of 451 patients, \*245
- Tuberculosis: See also under special structures of eye and names of diseases  
pathogenesis and treatment of retinal detachment of tuberculous origin, 362  
pseudotumors of macula, 89  
studies in experimental ocular tuberculosis; effect of "promin" and "promizole" in experimental ocular tuberculosis in normal rabbit, \*1  
studies in experimental ocular tuberculosis; effect of streptomycin and "promizole" on experimental ocular tuberculosis in immune-allergic rabbit, \*413
- Tularemia, primary and secondary changes in eye in, 354
- Tumors: See also Adenoma; Granuloma; Melanoma; Nyoblastoma; Retinoblastoma; etc.; and under names of organs and regions, as Cranium; etc.  
dermoid and epidermoid, of orbit, \*639
- Tunica Vasculosa Lentis: See Lens, Crystal-line
- Twilight Vision: See Vision
- Twins; extensive symmetrical cerebral calcification and chorioretinitis in identical twins (toxoplasmosis?), 222
- Tyloma, types and variants of epibulbar epitheliomas; typical invading and cachexia-producing epithelioma and barely malignant epithelioma arising from Keratoconjunctiva (tyloma), 363
- Typhoid; treatment of staphylococcic corneal ulcerations with antitoxin, 80
- Ulcers, Corneal: See Cornea, ulcers
- Ultraviolet Rays: See Light
- Unsworth, A. C.: Retrolental fibroplasia; preliminary report, \*341
- Urethritis: See Reiter's Disease
- Uvea; acute neuropathic necrosis of, \*112  
Inflammation: See also Ophthalmia, sympathetic  
inflammation; nonperforating thermometric cyclodiathermy in treatment of hypertensive uveitis, \*509  
influence of hypersensitivity on endogenous uveal disease, 232  
migrating ciliary nodules on retina, 230  
necrosis caused by circulatory disturbances (cyclodialysis), \*102  
necrosis of ciliary body, \*117
- Uveitis: See Uvea, inflammation
- Vasa Hyaloidea Propria: See Vitreous Humor
- Vasomotor System: See Arteries; Blood, pressure; Blood Vessels
- Veasey, C. A., Jr.: Dissatisfied refraction patient, 97
- Verhoeff, F. H.: Successful diathermy treatment of recurring retinal hemorrhage and retinitis proliferans; report of case, \*239
- Veins, Retinal: See Retina, blood supply; Thrombosis
- Veterans; delayed keratitis due to mustard gas (dichlorodiethyl sulfide burns); report of 2 cases, \*291
- Vision: See also Accommodation and Refraction; Blindness; etc.  
alterations of visual fields in tobacco amblyopia, 368  
central visual field after occipital lobectomy, 226  
Color: See Color Blindness  
Defective: See Phorias; etc.  
diseases of brain and optic nerve; concentric restriction of vision from unilateral cerebral lesions, 226  
fixation light, \*351  
in strabismus; preliminary report, \*438  
localizing value of visual fields in patients with early chiasmal lesions, \*579  
perimetric charts in equivalent projection, allowing planometric determination of extension of visual field, 225  
Tests: See also Accommodation and Refraction  
tests; "duction test"; evaluation of various technics, 90  
twilight vision and vitamin A, 364  
visual disturbances due to digitals, 85
- Vitamins: See also Ascorbic Acid; Thiamine; etc.  
A, and twilight vision, 364  
A; xerophthalmia and keratomalacia in children, 220  
B; experimental studies in retrobulbar neuritis, 229  
B<sub>1</sub>: See Thiamine  
K, use in treatment of intraocular hemorrhages, 368  
P: See Flavones
- Vitreous Humor; necrosis of vitreous and zonule, \*117  
ocular changes associated with scrub typhus; study of 451 patients, \*245  
substitution of cerebrospinal fluid for vitreous clouded with opacities, 365  
use of roentgen therapy for retinal diseases characterized by new-formed blood vessels (Eales's disease; retinitis proliferans); preliminary report, \*389
- War: See also Military Medicine; etc.  
ophthalmology during war and in future, 85, 223
- Water; cornea; swelling properties of fibrous tunic of eye, \*601
- Weekers, L.: Nonperforating thermometric cyclodiathermy in treatment of hypertensive uveitis, \*509
- Weekers, R.: Nonperforating thermometric cyclodiathermy in treatment of hypertensive uveitis, \*509

- Weil-Felix Reaction: See Trachoma
- Weiss, C.: Experimental investigation of pathogenicity of diphtheroids isolated from human conjunctiva, \*23
- Wood, R. M.: Studies in experimental ocular tuberculosis; effect of streptomycin and "promizole" on experimental ocular tuberculosis in immune-allergic rabbit, \*413
- Woods, A. C.: Studies in experimental ocular tuberculosis; effect of "promin" and "promizole" in experimental ocular tuberculosis in normal rabbit, \*1
- Woods, A. C.—Continued  
Studies in experimental ocular tuberculosis; effect of streptomycin and "promizole" on experimental ocular tuberculosis in immune-allergic rabbit, \*413
- Xerophthalmia and keratomalacia in children, 220
- X-Rays; See Roentgen Rays
- Zentmayer, W.: H. Maxwell Langdon, 235
- Zonule of Zinn; necrosis of vitreous and zonule, \*117
- Z-Plastic Operation: See Plastic Surgery

